Efficacy, Safety and Epidemiology of Anti-Obesity Drug Prescribing in Children and Adolescents

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Plagiarism Statement

This thesis describes research conducted in the UCL School of Pharmacy, between 2007 and 2012 under the supervision of Professor Ian Wong and Professor Russell Viner. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

30/11/2015

Signature Date

Abstract

Three drugs were approved for obesity treatment in the UK between 1998 and 2006: orlistat, sibutramine, and rimonabant; however the latter two drugs were withdrawn from the market. The National Institute for Health and Clinical Excellence guidelines (NICE) issued in recommended that anti-obesity drugs were appropriate for obesity management in children and adolescents aged ≥ 12 years in certain circumstances. Currently, there is little evidence on drug use for obesity treatment in young people in the UK.

From a meta-analysis of RCTs, after 6 months of treatment, orlistat together with behavioural therapy reduced body mass index (BMI) by 0.83 mg/m^2, with a high number of gastrointestinal adverse drug reactions (ADRs). Sibutramine with behavioural therapy reduced BMI by 2.20 mg/m^2. Between 1999 and 2006, the use of anti-obesity drug in primary care increased 15-fold. Approximately 45% of orlistat and 25% of sibutramine prescriptions were discontinued after one month of treatment. This may indicate that these drugs were not effective or poorly tolerated in children.

A meta-analysis of 12 RCTs on metformin has shown a BMI reduction by 0.64 mg/m^2 in obese young people without diabetes. A cohort study from a paediatric obesity clinic has shown that metformin was the most commonly prescribed drug. Metformin together with lifestyle intervention was shown a small but statistically significant effect on reducing the BMI standard deviation score in girls compared to lifestyle intervention alone after 6 months of treatment.

The questionnaire study shows that over half of GPs who initiated drug prescriptions to obese young patients did not consult specialists for advice. Despite NICE guidance, GPs expressed a need to have an obesity guidance covers pharmacological and non-pharmacological interventions.

As there is increased use of metformin for obesity treatment, in both primary and secondary care, clinicians should use the most up-to-date evidence when prescribing metformin for treatment in young people.

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Publications

To date, the results of this thesis have been presented on the following occasions:

Peer-reviewed journals

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Hsia Y, Neubert AC, Viner RM, Wong, ICK (2008). Dramatic rise in anti-obesity drug prescribing in children and adolescents: a population-based study in the UK. *Pharmacoepidemiology and Drug Safety*, 17:s140.

Table of Contents

List of Tables

List of Figures

Glossary of Terms

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
AMR	Acceptable mortality reporting
BMI	Body Mass Index
BMI SDS	Body Mass Index Standard Deviation Score
BNF	British National Formulary
BNF-C	British National Formulary for Children
BORIS	Business Objects Replacement Information System
BO	Business Objects
CDC	Centres for Disease Control and Prevention
CHD	Coronary Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPPR	Centre for Paediatric Pharmacy Research
DIN	Doctors' Independent Network
DoH	Department of Health
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FF-GPRD	Full Feature General Practice Research Database
GMS	General Medical Service
GP	General Practitioner
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
HSE	the Health Survey of England
ICD-10	International statistical Classification of Diseases and related health problems
IMD	Index of Multiple Deprivation
IMS DA	IMS Disease Analyzer-Mediplus database
IOTF	International Obesity Task Force
IQR	Interquartile range

MD	Mean Difference
MEMO	Tayside Medicines Monitoring Unit
MHRA	Medicines and Healthcare products Regulatory Agency
MSGP4	The Fourth Survey of Morbidity in General Practice
NCHS	National Center for Health Statistics
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NSHG	National Study Health and Growth
OGTT	Oral Glucose Tolerance Test
ONS	Office for National Statistics
OSCA	the Obesity Services for Children and Adolescents network
OTC	Over the counter
OXMIS	Oxford Medical Information System
QOF	the Quality and Outcome Framework
QUOROM	The Quality of Reporting of Meta-analyses
PCOS	Polycystic ovarian syndrome
PCT	Primary Care Trust
PPA	Prescription Pricing Authority
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMISE	Paediatric Research in Obesity Multi-model Intervention and Service Evaluation
RCT	Randomised controlled trial
RIO	the Rimonabant in Obesity programme
SD	Standard Deviation
SE	Standard Error
SEAG	Scientific and Ethical Advisory Group
SIGN	Scottish Intercollegiate Guidelines Network
SPC	Summary of Product Characteristics
SSRIs	Selective serotonin reuptake inhibitors
THIN	The Health Improvement Network
UK	United Kingdom
US	United States (of America)

UTS	Up-to-standard
VAMP	Value Added Medical Products
WHO	World Health Organisation
Young people	Children or adolescents aged 18 years or younger

Chapter 1 Introduction

1.1. Definition of childhood obesity

Obesity is a common nutritional disorder in young people. Childhood obesity has significantly increased over the years, which has caused serious public health concerns worldwide. The World Health Organisation (WHO) estimated that nearly 40 million children aged under five years were overweight in 2010 (WHO, 2012). According to the WHO, obesity is defined as abnormal or excessive fat accumulation that may impair health. It is normally caused by two main factors: unhealthy diet (e.g. excess intake of sugars, fats, carbohydrates) and lack of physical activity.

The most commonly used measure of obesity is the body mass index (BMI), which is a fairly accurate measure of an individual's body weight in relation to their height, and is calculated as: weight in kilograms divided by the square of height in metres (kg/m^2). BMI is an indicator to assess weight status in adults as well as in children. In adults, the cut-off points to define overweight and obesity are not related to age and sex. However, the weight and height of children and teenagers varies continuously with age and differs for boys and girls. BMI in children and adolescents can be expressed as a BMI centile; the centile is normally used to assess the growth patterns of individual children in relation to an age- and sex-matched reference population. These reference populations describe the growth patterns for children at different ages and by sex, and have normally been compiled using data from healthy paediatric populations (Wright *et al*., 2002).

Four growth reference charts have been widely used in the UK: the Tanner-Whitehouse (TW), Gairdner-Pearson (GP), Buckler-Tanner (BT) and the UK 1990 (UK 90). Confusion as to which reference chart should be used led the Royal College of Paediatrics and Child Health (RCPCH) to persuade the Growth Reference Review Group to provide advice on validity and comparability of these reference charts. The review group recommended that the UK 90 was the only suitable reference chart to assess weight relative to height (Wright *et al*., 2002). The UK growth chart weight categories and the corresponding centiles are shown in the below table:

Table 1.1: The UK 90 growth chart reference weight categories

BMI classification	BMI centile range
Underweight	< 2^{nd} centile
Healthy weight	>=2^{nd} to <85^{th} centile
Overweight	>=85^{th} to <95^{th} centile
Obese	>=95^{th} centile

The degree of obesity can also be expressed using BMI standard deviation score (BMI SDS) above the mean i.e. BMI at 50^{th} centile for age and sex. BMI SDS is also known as BMI z-score; the z-score expresses the number of standard deviations away from the population mean. The BMI SDS is calculated as:

$$\text{BMI SDS} = (V-M)/S$$

where V is the value of the individual's body weight and M is the mean of BMI value for age in boys and girls. S is the standard deviation (SD) for that mean value (Hall & Cole, 2006). BMI SDS can be used to classify the degree of overweight/obesity of a child's weight status. For example, a child having a BMI SDS of 2 or more (2/more SD above mean value) is considered obese (Kiess *et al*., 2004).

Another concern for BMI measurement in children is defining the cut-off points to define overweight and obesity. Adults with a BMI value of 25kg/m^2 are defined as overweight and those with a BMI of 30 kg/m^2 as obese; this definition in the adult population is internationally recognised. However, as the BMI measurement varies with age and sex in children the adult cut-off points cannot be applied to children and adolescents. Two international references have been used to define overweight and obese children: the International Obesity Task Force (IOTF) reference (Cole *et al*., 1995) and the WHO standard (de Onis *et al*., 2004). The IOTF reference is based on data from six countries (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore and the USA); a total number of 97,876 boys and 94,851 girls are included from birth to 25 years old. The WHO standard is derived from six countries (Brazil, Ghana, India, Norway, Oman and the US) with a sample of 26,985 children, aged 18-71 months (de Onis *et al*., 2004). Those children with a BMI greater than the 85^{th} centile of the reference population are considered at risk of being overweight according to the WHO definition, which is the same as the UK90 chart.

In the United States (US), the Center for Disease Control and Prevention (CDC) chart is based on height and weight data produced by the US National Center for Health Statistics (NCHS). The US age- and sex-specific BMI centile chart for children and adolescents aged 2-20 years has been used worldwide. It defines a BMI greater than 95th centile of the US reference population as a cut-off point for obesity in children. At present, the WHO recommends the NCHS/CDC age- and sex-specific BMI centile chart to determine young people who are overweight and obese (Lahti-Koski *et al*., 2004). However, a national BMI centiles chart (Figure 1.1 & Figure 1.2) derived from the UK 1990 growth reference curves is available (Cole *et al*., 1995). Based on this reference, obesity in children in the UK is defined as a BMI $\geq$98th centile. In general, a BMI between the 5th-84th centile is defined as a healthy weight. It has been suggested that if the aim is to identify severely obese young people, the cut-off points should be set between the 98th or 99.6th centile, as these individuals may be aware of their obesity and should be considered candidates for intervention (Hall & Cole, 2006).

Figure 1.1: UK childhood BMI centile charts: BMI chart for boys

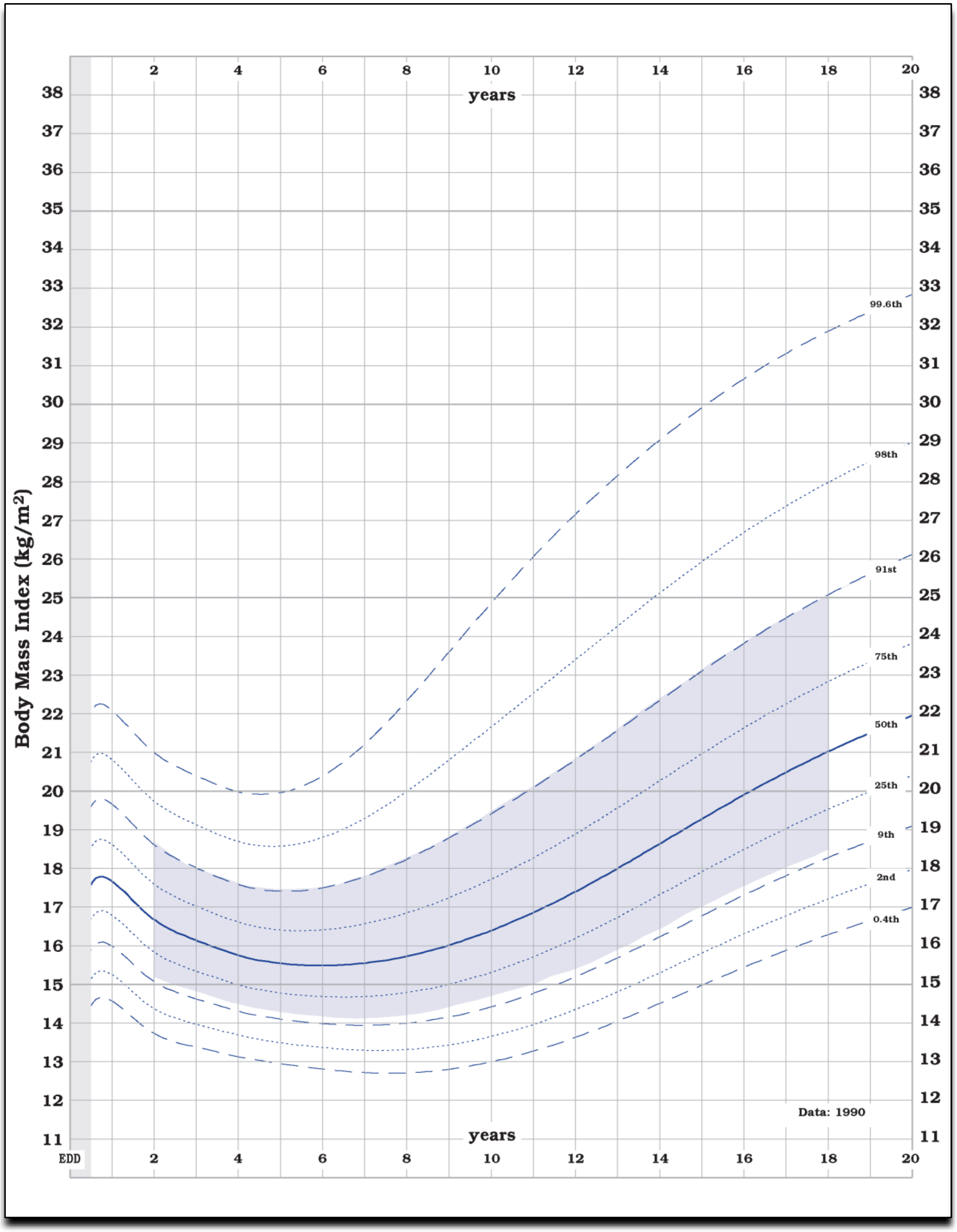

Figure 1.2: UK childhood BMI centile charts: BMI chart for girls

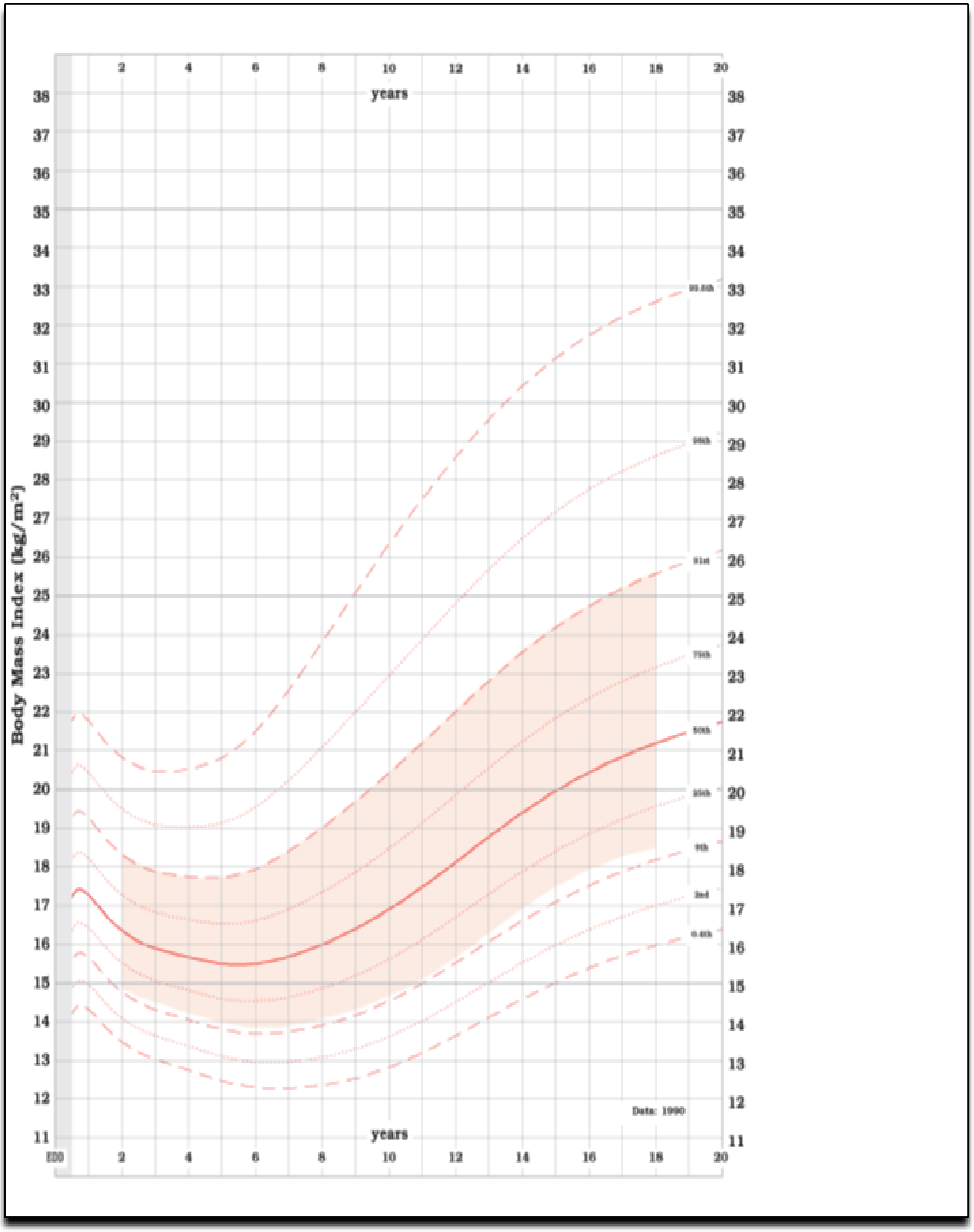

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Table 1.2 illustrates the different BMI cut-off criteria used to define overweight and obese children in these charts. Currently, there is no compelling evidence to show which cut-off point should be used to determine normal and abnormal BMI in young people (NICE, 2006; Monasta *et al*., 2011). In addition, many countries have developed their own BMI centile charts and selected different cut-off points to define overweight and obesity, further complicating the BMI for childhood obesity issue (Hall & Cole, 2006). The discussion on selection of an appropriate reference population and cut-off points in BMI centiles in order to define weight status in obese young people is on-going (Monasta *et al*., 2011).

As discussed, the BMI cut-off point for defining childhood obesity is somewhat unclear at present. The different cut-off criteria would affect the number of children screened into different obesity categories (Livingstone, 2001), and also affect the advice given in regard to obesity treatment (Hall & Cole, 2006). Furthermore, different cut-off criteria make it difficult to directly compare the prevalence of overweight and obese children in different countries (Livingstone, 2001; Wang & Lobstein, 2006; Monasta *et al*., 2011). The issue of defining the BMI cut-off criteria is beyond the scope of this project, nevertheless the BMI centile charts for age is an acceptable tool to assess adiposity in childhood obesity worldwide (Hall & Cole, 2006).

Table 1.2: BMI cut-off points for overweight and obesity definition in children (modified from Poskitt & Edmunds, 2008)

	Centile			
	Overweight	Obesity	Growth standards used	Reference
1990 UK BMI reference charts	>91st	≥98th	UK	Scottish Intercollegiate Guidelines Network (SIGN, 2010); National Institute for Health and Clinical Excellence (NICE, 2006).
WHO standard	91st	98th	BMI standard based on 26985 children records from Brazil, Ghana, India, Norway, Oman, and United States.	WHO Multicentre Growth Reference Study (MGRS) (de Onis *et al*., 2004)
IOTF	≥90th and ≤97th	>97th	International comparison: children in United Kingdom, Hong Kong, Singapore, Brazil, the Netherlands, United State.	Cole *et al*., (2000)
CDC[b]	>85th	≥95th	USA	Must & Anderson (2006)

Abbreviation: WHO, World Health Organisation; IOTF: International Obesity Task Force; CDC: Center for Disease Control.

1.2.Epidemiology of childhood obesity

The obesity epidemic in young people has increased globally. As mentioned earlier, direct comparison of prevalence of childhood obesity between countries is difficult since different criteria are used to define obesity and being overweight in young people. Data from national and regional studies on the prevalence of overweight and obese children and adolescents have been published over the years. Table 1.3 illustrates the global trend of prevalence of overweight and obesity in school-aged children (Wang & Lobstein, 2006). It clearly shows that the prevalence of overweight and obesity varies between countries; this is mainly due to different definitions of overweight and obesity used in studies. From this global trend between the 1970s and late 1990s, the prevalence rates of overweight and obese children and adolescents have shown a steady increase.

In Europe, it has been estimated that approximately 15 million children and adolescents will be overweight and obese by 2010 if obesity continues to increase at the same rate as in the 1990s (Branca *et al*., 2007). In 2007, Branca's team reported that the highest prevalence rates of overweight children were in Portugal (aged 7-9, 32%), followed by Spain (aged 2-9, 31%), and Italy (aged 6-11, 27%) in both sexes. The lowest rates of overweight prevalence of children were Germany (aged 5-6, 13%), Cyprus (aged 2-6, 14%), and Serbia and Montenegro (aged 6-10, 15%). However, it should be noted that different socioeconomic groups, cultural determinants of diet and physical activity may have an impact on the prevalence of obesity in these European countries.

Table 1.3: Worldwide trends of overweight and obesity prevalence in school-age children (reproduced from Wang & Lobstein, 2006)

Country	Date of survey	Criteria of definition	Age (years)	Prevalence of Obesity (%)	Prevalence of Overweight and obesity (%)	Sample size	National or local survey
North/South America							
Canada	1981;1996	IOTF	7-13	Boys: 2.0→10.0 Girls: 2.0→9.0	Boys: 11.0→33.0 Girls: 13.0→27.0	1981: 2879 1996: 6277	N
Chile	1987;2000	IOTF	6	Boys: 1.8→7.2 Girls: 2.1→7.5	Boys: 10.6→18.8 Girls: 11.6→19.6	1987: 166,891 2000:199,444	N
United States	1971-1974 1988-1994	IOTF	6-18	INA	15.4→25.6	1971-1974: 4472 1988-1994: 6108	N
United States	1971-1974 1999-2000	CDC	6-19	6-11y: 4.0→15.3 12-19y: 6.1→15.5	INA	1971-1974: INA 1999-2000: 3298	N
Europe							
Czech Republic	1991;2000	Czech 90th/97th centiles chart	7-11	3.0-6.0	10.0-13.0	3343	N
Finland	1977;1999	IOTF	12-18	Boys: 1.1→2.7 Girls: 0.4→1.4	Boys: 8.3→19.4 Girls: 4.5→11.2	1977:2832 1997:66,211	N
France	1980;1990		4-17	2.5-3.2	10.0→11.7	1980:6697 1990:5795	N
France (North)	1992;2000	IOTF	5-12	Boys: 1.7→1.3 Girls: 1.6→4.4	Boys: 9→10.2 Girls: 14.1→18.6	1992: 804 2000: 601	L
Germany	1985;1995	BMI 90th/97th centiles chart	7-14	Boys: 5.3→8.2 Girls: 4.7→9.9	Boys: 10.0→16.3 Girls: 11.7→20.7	1985: 2002 1995: 1901	L
Greece (Crete)	1982	IOTF	11-13	Boys: 4.2-12.7	Boys: 20.6-39.7	1982:528 2002:620	L
Iceland	1978;1998	IOTF	9	Boys: 1.8→5.8 Girls: 0.5→4.2	Boys: 12.4→22.0 Girls: 11.9→25.5	1978: 418 1998: 601	N
The Netherlands	1980 1996-1997	IOTF	9	Boys: 0.1→1.1 Girls: 0.5→1.9	Boys: 3.3→9.0 Girls: 6.8→13.2	Approx. 700	N
Poland	1987;1997	Local BMI 85th/95th centiles chart	14	8.4→9.7	23.8→22.1	1987: 3165 1997: 1014	L
Spain	1985;1995	IOTF	6-7 13-14	Children Boys: 6.5→14.2 Girls: 10.0→17.7 Adolescents Boys: 3.1→6.0 Girls: 1.1→1.5	Children Boys: 21→34 Girls: 25→36 Adolescents Boys: 13→21 Girls: 16→21		
Sweden	1986;2001	ITOF	6-13	1.2→4.8	11.5→23.1	1986: 507 (aged 6-11) 2001: 1115 (aged 6-13)	L
United Kingdom	1984;2002	ITOF	4-11	Boys: 1.7→5.4 Girls: 2.6→7.8	Boys: 9.0→20.7 Girls: 13.5→27.4	1984: 5874 (aged 4-11) 2002: 9982 (aged 2-10)	N
Northern Ireland	1990;2000	ITOF	12	Boys: 4.0→4.7 Girls: 1.6→4.7	Boys: 16.0→19.5 Girls: 15.9→26.3	1990: 509 2000: 1047	N
Australia							
Australia	1985;1995	ITOF	7-15	Boys:1.4→4.7 Girls: 1.2→5.5	Boys:10.7→20.0 Girls: 11.8→21.5	1985:8492 1995:2962	N

Continued.

Asia							
China, mainland	1991:1997	ITOF	6-18	INA	All: 6.4→7.7 Urban: 7.7→12.4 Rural: 5.9→6.4	1991: 3014 1997: 2688	N
China, mainland	1985:2000	China BMI	7-22	Urban Boys: 1.1→10.4 Girls: 0.2→2.3 Rural Boys: 0.04→1.5 Girls: 0.06→0.9	Urban Boys: 1.3→14.8 Girls: 1.7→8.3 Rural Boys: 0.5→5.8 Girls: 1.7→4.7	1985: 4,71,115 2000: 2,66,431	N
Taiwan	1980-1982 1994-1996	≥110% local and ≥ 120 BMI reference	12-15	Boys: 12.4→16.4 Girls: 10.1→11.1	Boys: 25.4→28.0 Girls: 21.4→21.3	1980-1982: 1980 1994-1996: 1366	N
Japan	1976-1980 1996-2000	≥ 120 local BMI reference	6-14	Boys: 6.1→11.1 Girls: 7.1→10.2	INA	1976-1980: 15,677 1996-2000: 6079	N
Japan	1976-1980 1996-2000	IOTF	6-14	Boys: 1.5→3.8 Girls: 1.2→2.9	Boys: 10.7→20.0 Girls: 10.1→17.2	1976-1980: 15,677 1996-2000: 6079	N
Singapore	1975:1993	≥ 120 local BMI reference	6-16	Boys: 1.6→15.2 Girls: 1.1→12.9	INA	INA	N

Abbreviation: INA: Information not available, N: national; L: Local ITOF: the IOTF age- and sex-specific BMI cut-off points that correspond to a BMI of 25mg/m^2 and 30mg/m^2 at age 18.

In the UK, data from the National Study of Health and Growth (NSHG) has shown that the prevalence of obesity increased from 0.6% in 1984 to 1.7% in 1994 in boys and from 1.3% to 2.6% in girls. The number of children defined as overweight also increased, for boys from 5.4% to 9.0% and for girls from 9.3% to 13.5% (Chinn & Rona, 2001). The report of a recent survey, the Health Survey of England (HSE) in 2008, found that the prevalence of obesity among boys aged 2-15 years, increased from 11.1% in 1995 to 16.8% in 2008, and the increase for girls in this age range was from 12.2% to 15.2%. However, there was a significant decrease in obesity between 2005 and 2008. The prevalence of obesity in boys decreased from 18.5% in 2005 to 16.8% in 2008 and from 18.8% to 15.2% in girls. It has been suggested that HSE should continue monitoring whether the overall trend in childhood obesity is decreasing or continuing to increase gradually (HSE, 2008). The most recent reports from HSE and the UK National Child Measurement programme have shown that the prevalence of childhood obesity has apparently plateaued (HSE, 2014; the UK National Child Measurement programme, 2014).

Current estimates have also shown that the prevalence of obesity in young people has levelled off in some countries. In Switzerland, a national survey included children aged 6-13 years and used US CDC cut-off points to define underweight, overweight, and obesity in the years 2002 (2,431 children) and 2007 (2,222 children). In 2002, the prevalence of being overweight in boys and girls was 12.5% and 13.2%, respectively. However in 2007, the prevalence of being overweight was significantly lower, 11.5% in boys and 10.0% in girls. Prevalence of obesity also decreased in both genders between 2002 and 2007 (Aeberli *et al*., 2010). In France, overall prevalence of being overweight (including obesity) using the IOTF in children aged 7-9 years was 18.1% in 2000 with a decrease to 15.8% in 2007 (Salanave *et al*., 2009). The authors stated that the stabilised trend may be due to the introduction of a National Nutrition and Health Program (PNNS) in 2001.

A German study analysed the CrescNet database, consisting of 462,241 patients aged 4 to 16 years from 321 paediatricians, to investigate the prevalence of overweight and obesity between 1999 and 2008. Prevalence of overweight and obesity increased between 1999 and 2003, but the trend declined significantly between 2004 and 2008 (Bluher *et al*., 2011). Data from monitoring overweight and obese children assessed at school enrolment examinations (SEE), also in Germany, were analysed. The SEE is an annual compulsory programme in Germany in which the weight and height of all children are measured at school enrolment. In December 2008, data were retrieved from 721,364 children aged 6 years in 16 federal states. The German reference cut-off points were used to define overweight (BMI $>90^{th}$ centile) and obesity (BMI $>97^{th}$ centile). Prevalence of overweight and obesity had decreased from 3% to 1.8% between 2004 and 2008 (Moss *et al*., 2012).

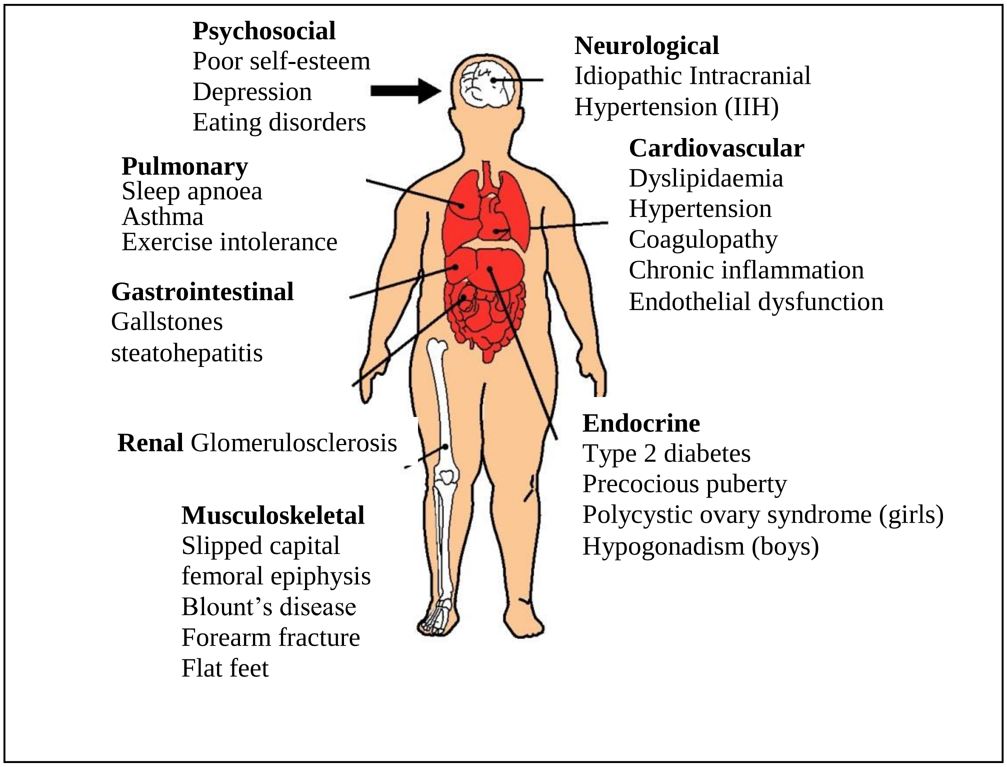
In Greece, data were analysed from 11 annual national school-based health surveys from 1997 to 2007. Height and weight were measured for 651,582 children aged 8-9 years, using IOTF BMI cut-off points to define underweight, normal weight, overweight and obesity. Prevalence of obesity significantly increased from 7.2% in 1997 to 11.3% in 2004 in girls. A similar increasing trend was also observed in boys from 8.1% to 12.3% during this period. However, the trend began to level in both genders from 2004 onwards (Tambalis *et al*., 2010). A systematic review and meta-analysis were undertaken to investigate the prevalence of childhood overweight and obesity in Australia. A total of 41 studies were included, which involved 264,905 children aged 2 to 18 years. The estimated prevalence of overweight and obesity in boys increased from 10.2% to 21.6% and from 11.6% to 24.3% in girls, between 1985 and 1996. However, the estimated prevalence has recently plateaued, with only a slight increase to 23.7% in boys and 24.8% in girls in 2008 (Olds *et al*., 2010).

A recent US study analysed 15,271 children and adolescents (from birth to 19 years) from the National Health and Nutrition Examination Survey (NHANES) to investigate the prevalence of obesity between 1999 and 2010. The CDC 2000 BMI-for-age growth chart was used to define overweight (BMI$\geq 85^{th}$ centile and $<95^{th}$ centile) and obesity (BMI$\geq$ 95^{th} centile). Overall, there was no change in obesity prevalence between 2007-2008 and 2009-2010 (Ogden *et al*., 2012). The explanations for this recent levelling in the trend of increasing obesity prevalence could be due to the increasing recognition by health professionals, schools, community programmes, and policy interventions or media coverage (Aeberli *et al*., 2010; Salanave *et al*., 2009; Tambalis *et al*., 2009; Olds *et al*., 2010; Moss *et al*., 2012). At present, there is no evidence to show which interventions accounted for this change in the trend. Further research is needed to understand why this increasing trend has levelled off in children and young people. Despite the apparent plateau in the prevalence of obesity, there is still growing concern that childhood obesity may lead to obesity related complications such as type 2 diabetes and/or, hypertension. These complications will subsequently contribute to the economic burden of treating these patients when they reach adulthood (Lobstein & Jackson-Leach, 2006; Branca *et al*., 2007). A brief review on obesity-related complications in children and adolescents is given in the following section.

1.3.Complications of childhood obesity

It has been suggested that overweight children are more likely to become obese adults (Loke, 2002). There is strong evidence that childhood obesity is a risk factor for several medical complications, which may lead to life-threatening conditions in adulthood (Wabitsch, 2000; Ebbeling *et al*., 2002; Ludwig, 2007; Wall, 2010) (Figure 1.3). A long-term study of 276,835 Danish school children (aged 7-13 years) which investigated the association between childhood obesity and coronary heart disease (CHD) in adulthood (aged 25 years or older), found that a higher BMI in childhood was associated with an increased risk of CHD in adulthood (Baker *et al*., 2007). It has been recently suggested that the prevalence of CHD will increase from 5 to 16% by the year 2035, which is attributable to the increased obesity in adolescents currently (Bibbins-Domingo *et al*., 2007). This association between childhood obesity and cardiovascular risk may increase premature mortality (Franks *et al*., 2010).

Figure 1.3: Medical complications of childhood obesity



Childhood obesity is strongly associated with other chronic conditions including metabolic syndrome, hypertension, type 2 diabetes, and a range of psychosocial dysfunctions. The association between type 2 diabetes and obesity in young people is another challenging issue in public health. The incidence rate of type 2 diabetes has significantly increased in children (Pinhas-Hamiel *et al*., 1996; Scott *et al*., 1997; Haines *et al*., 2007). A study by Fagot-Campagna *et al*., (2000) found that type 2 diabetes was more common than type 1 diabetes among 45% of newly diagnosed diabetic Indian adolescents aged 15-19 years in the US, during the years 1976-1976, and also during 1987-1996. In the UK, the prevalence of type 2 diabetes in adolescents dramatically increased from 0.006 per 1000 children in 1998 to 0.05 per 1000 children in 2005; the prevalence increased with age especially among adolescents aged 12-18 years (Hsia *et al*., 2009). There is strong evidence that the rise of type 2 diabetes in young people is mainly due to increasing levels of obesity in young people (Ebbelling *et al*., 2002; Han *et al*., 2010).

The obstructive sleep apnoea syndrome is another serious condition amongst obese young people (Loke, 2002). This syndrome is the result of excessive fat in the neck which consequently causes partial obstruction of the upper airway during sleep. During the past few years, this syndrome has become widely recognised as a serious obesity related condition in children (Tauman & Gozal 2006). The poor quality of sleep at night will consequently result in morning headache and daytime sleepiness and it also affects their daily functioning (e.g. learning and school performing) (Gozal, 1998). Psychological problems are also common in overweight and obese young people. Obese children and adolescents may encounter discrimination at an early age. Viner *et al*., (2006) reported that approximately 13% of obese adolescents suffered from psychological distress in the UK. A Canadian study included 5,749 boys and girls aged 11 to 16 years to investigate the association between bullying behaviours (physical, verbal, relational and sexual harassment) with overweight and obesity status (Janssen *et al*., 2004). Their findings have shown that overweight and/or obese boys and girls were likely to have verbal, physical and relational bullying compared with their normal weight peers. A recent systematic review which examined the association between obesity and depression using data from published prospective cohort studies found that obesity increased the risk of depression (Luppino *et al*., 2010).

There is economic burden for covering the treatment of obesity-related complications in young people. A US study examined the economic cost of treating obesity-related conditions in young people aged 6-17 years during 1979 and 1999 (Wang & Dietz, 2002). Their results have shown that hospital costs for treating obesity-related complications increased from $35 million during 1979-1981 to $127 million during 1997-1999, increasing more than threefold during a twenty-year period. Due to the current obesity epidemic in children and adolescents, there will be a significant increase in physical, psychological, and economic consequences in the near future. These obesity-related complications mean urgent action needs to be taken by healthcare professionals to improve the quality of life of overweight and/or obese children and adolescents.

1.4.Management of childhood obesity

It has been recommended that the successful management of obesity should be through lifestyle changes including diet modification and increased physical activity (Iughetti *et al*., 2011). Since obesity may cause other medical conditions such as psychosocial problems and increased risk of mortality, it is recommended that multidisciplinary interventions are appropriate for childhood obesity management (Epstein, 2001). It has been suggested that the multidisciplinary team may include the GP, practice nurse, health visitor, school nurse and other professionals such as a dietician, and psychologist (Gibson *et al*., no date). Multi-component intervention for childhood obesity is also recommended by UK national guidelines (NICE, 2006; SIGN, 2010). The multi-component intervention includes diet (e.g. decreased fat intake, increased fruit and vegetable intake), increased physical activity, behaviour interventions (e.g. goal setting, rewards for reaching goals), and family involvement (NICE, 2006).

A systematic review examined 37 RCT trials on effectiveness of dietary intervention in obese young people (aged <18 years) from 1975 to 2003 (Collins *et al*., 2006). However, the authors concluded that due to poor study design, it was difficult to assess the effectiveness of dietary intervention in obese young people. Collins and colleagues (2007) conducted another systematic review to investigate the optimal dietetic treatment for overweight and/or obese young people (aged <18 years). Studies which evaluated the effectiveness of nutrition or dietary interventions for treating obesity were all included. They included all types of study designs: RCTs, longitudinal studies, cohort (retrospective and prospective), or case-control studies. In addition, government reports from the UK, US, and Australia were included in the review. A total of 116 studies were identified between 1975 and 2003 in the final review, of which 49 (42%) studies were of RCT design. However, as the dietary outcomes of included studies were rarely reported, the authors stated that there was an urgent need to have well-designed studies to address the efficacy and effectiveness of dietary interventions in children and adolescent. At present, there is no evidence to suggest which particular dietary intervention is more effective for weight management in young people.

In 2004, a national report from the Department of Health in the UK suggested that the general population of children and adolescents should have at least 60 minutes of moderate intensity physical activity each day (DoH, 2004a). The NICE guidelines on obesity management (NICE 2006) also recommended that an increase of physical activity levels or a decrease of inactivity should be included in a multi-component interventions programme.

Behavioural intervention is part of a multi-component interventions programme. The NICE guideline (2006) suggested that a behavioural intervention must include: stimulus control, self-monitoring, goal setting, rewards for reaching goals, and problem solving. In Scotland, there was a RCT study that investigated behavioural intervention for obesity in children in the UK (Hughes *et al*., 2008). This study was conducted at the Royal Hospitals for Sick Children in Glasgow and Edinburgh, Scotland. A total of 134 overweight children (BMI ≥98th centile according to British 1990 reference data) aged 5-11 years were included. Children were randomly assigned to either the behaviour programme (intervention group) or standard care (control group). Behaviour intervention included modifying diet, changes in physical activity, and behavioural change techniques (e.g. to enhance the child's motivation, goal getting, self-monitoring, use of rewards) as well as standard care in the intervention group. Children in the control group received normal dietetic care. The findings showed that the behaviour programme had modest benefits on physical activity, sedentary behaviour, and quality of life (QoL). However, there was no significant difference between the intervention and control groups on BMI SDS, and weight over 12 months of treatment. For children who complied well with treatment, their weight gain was significantly lower in the intervention group compared with the control group, from baseline to 6 months. Another recent multicomponent, community-based childhood obesity intervention (Mind, Exercise, Nutrition, Do it (MEND) Program) RCT was conducted to investigate the effectiveness of a 6-month intervention. This program also engaged with families in the process of weight management. The interventions consisted of nutrition sessions (e.g. nutrition education, healthy eating advice), behaviour change sessions (to teach parents and children to apply behaviour techniques e.g. goal setting, stimulus control), and exercise sessions (included 1 hour of exercise). A total of 116 obese children (BMI ≥ 98th centile according to British 1990 reference data) were included and randomly assigned to intervention. The following outcomes were assessed at baseline and at 6 months: waist circumference, BMI, body composition, physical activity level, sedentary activities, cardiovascular fitness, and self-esteem. All children were followed up 12 months from baseline. Children in the intervention group had a statistically significant reduction in waist circumference z-score and BMI z-score compared to control group at 6 months. In addition to significant improvements in adiposity, the intervention also improved cardiovascular health and psychological well-being (Scher *et al*., 2010). In most contemporary RCTs of lifestyle interventions for childhood obesity treatment, there is at least one parent or carer involved in the treatment programme, with the aim of changing the whole family's lifestyle (SIGN, 2010). For example, the recommendation from 2006 NICE guideline for diet intervention should be multi-component, including dietary modification, targeted advice, family involvement and goal setting.

In general, overweight young people can be managed in the community by a primary care team. However, patients should be referred to specialists in secondary care for further assessment if they are extremely obese individuals with severe obesity-related co-morbidities (NICE, 2006). Figure 1.4 shows the childhood obesity management pathway in primary care and secondary care within the National Health System (NHS) (NICE 2006). The 2010 SIGN guidelines adopted the advice from the US Expert Committee of criteria for referral to a hospital general paediatric clinic for obese and/or overweight children and young people. The recommendations from SIGN guidelines are given below:

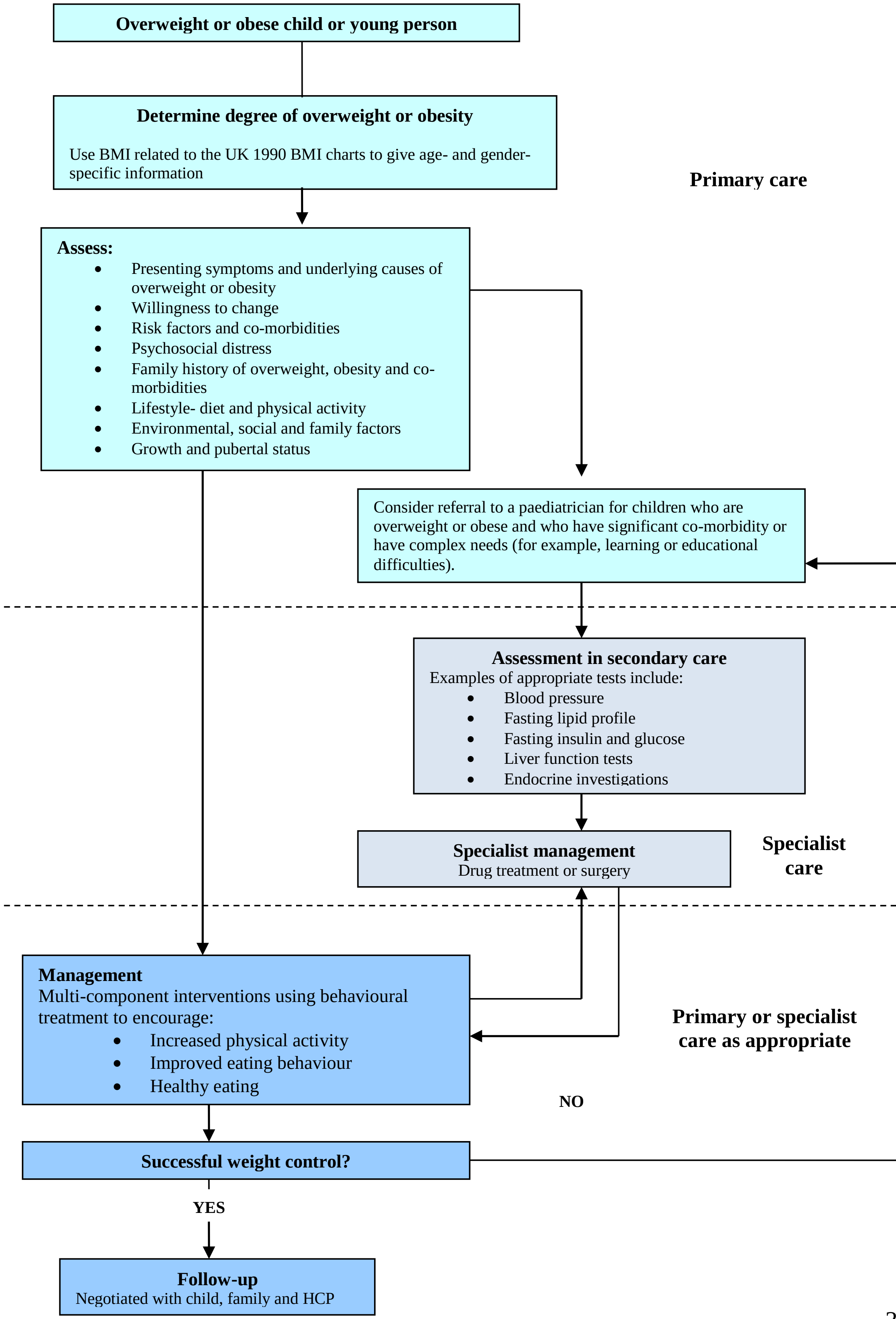
1) Children who may have serious obesity-related morbidity that requires weight loss (e.g. benign intracranial hypertension, sleep apnoea, obesity hypoventilation syndrome, orthopaedic problems and psychological morbidity).
2) Children with a suspected underlying medical (e.g. endocrine) cause of obesity including all children aged 24 months of age who are severely obese (BMI $\geq 99.6^{th}$ centile).

Recently, the Obesity Services for Children and Adolescents (OSCA) network released guidance on assessing childhood obesity in secondary care (Viner *et al*., 2012). The OSCA guidance provided more clear and detailed criteria for patient referral to secondary care compared to the NICE and SIGN guidelines. The OSCA criteria for patient referral to secondary care are given below:

1) There is a possibility of secondary obesity
    - Short stature for genetic potential/poor growth
    - Dysmorphisms
    - Learning difficulties
2) A likelihood of co-morbidity:
    - Hypertension
    - Symptoms of sleep apnoea
    - Acanthosis nigricans
    - Evidence of polycystic ovary syndrome (PCOS)
    - Psychological morbidities
    - Child safeguarding concerns
    - Biochemical evidence of impaired glucose tolerance: dyslipidaemia, liver dysfunction
    - Family history in close relatives: type 2 diabetes before 40 years or cardiovascular disease before 60 years

In the NHS clinical pathway for childhood obesity management, drug treatment and surgery should be initiated by specialists in secondary care. Drug treatment is not recommended in children younger than 12 years old, except for children with life-threatening co-morbidities. Drug treatment for obese and/or overweight children and adolescents is discussed in the next section. To date, there is much evidence to support efficacy of bariatric surgery in obese young people but less on safety issue (Michalsky *et al.,* 2014). It is not recommended as the first line choice of intervention in overweight young people. National guidelines recommend that bariatric surgery is only used for those who have a BMI ≥35mg/m^2 with serious obesity related co-morbidities, or BMI ≥40mg/m^2 with minor co-morbidities of obesity, the same guidelines as for adults (NICE, 2006; SIGN, 2010).

Figure 1.4: The UK clinical care pathway for children and young people with overweight and obesity (NICE 2006)



1.5.Pharmacological treatment in childhood obesity

As discussed earlier, pharmacological treatment should not be viewed in isolation in childhood obesity management in clinical practice. Pharmacological treatment is considered to be an appropriate approach for paediatric patients with BMI ≥30kg/m^2 with no obesity related risk factors and patients with BMI ≥27mg/m^2 with obesity-related complications, along with lifestyle modification (e.g. diet, exercise) (Ioannides-Demos *et al*., 2005). In general, the potential pharmacological agents for obesity treatment broadly fall into four categories: 1) drugs that stimulate anorexigenic signals (e.g. agonists of 5-HT receptors), 2) drugs that inhibit orexigenic signals (e.g. somatostatin analogues), 3) gastrointestinal peptides (e.g. oxyntomodulin analogues), 4) drugs that increase energy expenditure (e.g. growth hormone receptor agonist) (Isidro & Cordido, 2010).

Ideally, an anti-obesity drug should decrease appetite, increase energy expenditure, and/or modulate insulin production with no serious adverse reactions and achieve a 5% loss of initial body weight as required by the FDA and a 10% weight loss required by the EMA (Elangbam, 2009; Heal *et al*., 2009). Unfortunately, over the past decades, several anti-obesity drugs have been reported to be associated with serious adverse reactions, and as a result most anti-obesity drugs have been withdrawn from international market. A review of previously withdrawn anti-obesity drugs, those currently still on the market, and drugs in the late-stage of clinical development is presented in Table 1.4. In 2000, phentermine was withdrawn after the Europe-wide review of the risk and benefits of anorectic agents/appetite suppressants. In December 2002, the MHRA (medicines) is reinstating the relevant marketing authorisations for phentermine in the European Union. (http://www.investorvillage.com/smbd.asp?mb=633&mn=37850&pt=msg&mid=12071773).

Table 1.4: Anti-obesity drugs withdrawn from the market, on the market, and in late-stage clinical development (adapted from Elangbam 2009; Heal *et al*., 2009; Heal *et al*., 2012)

Drug	Trade name	Year of approval	Mechanism of action	United States	European Union
Phentermine	Lonamin®, Duromine®	1959	NE, and DA reuptake inhibitor	Marketed	Withdrawn 2000 and reinstated 2002
Diethylpropion	Tenuate®, Apisate®	1959 in US	NE and DA reuptake inhibitor	Marketed	Withdrawn 2000
Fenfluramine	Ponderax®, Pondimin®	1973 in US	5-HT releaser and reuptake inhibitor	Withdrawn 1997	Withdrawn 1997
Dexfenfluramine	Redux®	1996	5-HT releaser and reuptake inhibitor	Withdrawn 1997	Withdrawn 1997
Orlistat	Xenical®	1998	Lipase inhibitor	Marketed	Marketed
Rimonabant	Acomplia®	2006	Cannabinoid CB_1 antagonist	Not approved	Withdrawn 2008
Sibutramine	Meridia®, Reductil®	1997 in US 2000 in Europe	NA and 5-HT reuptake inhibitor	Withdrawn 2010	Withdrawn 2010
Topiramate/phentermine	Qnexa®	2012	NA and DA releasing agent	Pre-registration*	Pre-registration
Bupropion/naltrexone	Contrave®	NA	DA reuptake inhibitor/opioid antagonist)	2014	Phase 3
Lorcaserin (APD356)	Lorqess®	Approved in US	5-HT_{2c} agonist	Marketed†	Phase 3
Zonisamide/bupropion	Empatic®	NA	DA reuptake inhibitor	Phase 2	Phase 2

Abbreviations: CB1, cannabinoid receptor type1; 5-HT2c, 5-hydroxytryptamine (serotonin) receptor 2C; NE, noradrenaline; DA, dopamine; NA, not available.
*FDA Advisory Committee recommends approval of Qnexa® for obesity treatment in adult on 22nd February 2012. † FDA Advisory Committee recommends approval of Lorqess® for obesity treatment in adult in June 2012.

These drugs presented in Table 1.4 were originally licensed only for use in adults. In the mid-1990s, fenfluramine and dexfenfluramine (serotonin agonist) were both withdrawn due to pulmonary hypertension (Hutchinson & Ryder, 2007). In 2006, rimonabant was approved by the European Medicines Agency (EMA) for obesity treatment. It has been reported that UK, Germany, and France were the highest consumers of rimonabant worldwide (MHRA, 2008). However, due to the increasing numbers of reports of psychiatric adverse reactions amongst patients taking rimonabant, the EMA recommended the suspension of marketing authorisation of rimonabant in Europe. In the US, the FDA did not approve rimonabant for obesity treatment due to safety concerns on anxiety, and depression (Heal *et al*., 2012). In 2010, sibutramine was withdrawn from both the US and European markets as the data from clinical trials indicated an increased risk of cardiovascular disease (e.g. heart attack and stroke) in adults (James *et al*., 2010).

Following the withdrawal of rimonabant and sibutramine, there is currently only one drug, orlistat (Xenical®), an inhibitor of gastric and pancreatic lipases, approved for the treatment of obesity in Europe. In the US, in addition to orlistat, there are two centrally acting drugs approved for short-term obesity treatment (≤12 weeks), phentermine and diethylpropion. Of these centrally acting drugs, phentermine is the most frequently prescribed anti-obesity drug in adults (Hutchinson & Ryder, 2007). In 2010, there were three drugs in the pre-registration phase: Qnexa®, Contrave®, and Lorqess®. All these drugs are centrally acting agents. On 22nd February 2012, the FDA's advisory Committee approved Qnexa® for obesity treatment in adults. However, Qnexa® is still at the pre-registration phase and has not been approved by the EMA for obesity treatment at present. In addition to Qnexa®, the FDA approved another drug for obesity treatment in adults: Lorcaserin (Lorqess®). A review by Chan *et al*., (2012) investigated the efficacy of lorcaserin for obesity treatment from 3 published RCTs in adults aged 18-65 years. The result from the meta-analysis has shown that lorcaserin treatment reduced body weight by 3.23 kg and a reduction of BMI by 1.16 kg/m^2 compared to placebo after one year of treatment in adults. However, there is currently no evidence of lorcaserin for obesity treatment in children and adolescents. In 2014, Bupropion/naltrexone (Contrave®) was approved by FDA for obesity treatment in adults. In the same year, FDA also approved liraglutide (Saxenda®) as a treatment option for chronic weight management for adults with

BMI ≥ 30 kg/m^2 or adults with BMI of 27 kg/m^2 who have at least one weight-related condition such as hypertension, type 2 diabetes or high cholesterol (dyslipidaemia) (FDA 2014).

At the time of commencement of this thesis, there were two FDA approved anti-obesity drugs for use in adolescents: orlistat for patients aged ≥ 12 (approved in 1999) and sibutramine for patients aged ≥ 16 years (approved in 1997) in the US (Barlow, 2007). According to the Summary of Product Characteristics (SPC), anti-obesity drugs (orlistat, sibutramine) are not approved for use in patients aged less than 18 years in the UK (*Orlistat* SPC 2012; *Sibutramine* SPC 2011). Also, the EMA has not approved any anti-obesity drugs for use in children and adolescents in Europe (Karres *et al*., 2011). However, the UK national guidelines (NICE, 2006; SIGN, 2010) recommended that pharmacological intervention (orlistat, sibutramine) can be considered for adolescents and for children younger than 12 years with life-threatening co-morbidities. Table 1.5 shows the 2006 NICE recommendations for use of anti-obesity drugs (orlistat, sibutramine) in children and adolescents. For children aged 12 years or older, drug treatment is only recommended if physical co-morbidities (e.g. orthopaedic problems or sleep apnoea) or severe psychological co-morbidities are present. Although lifestyle and behavioural modifications, diet, and exercise are recommended as first line treatment for weight loss, there is still a need for pharmacological intervention as adjunctive therapy in real life (Karres *et al*., 2011). Given the short-term beneficial effects of the available drugs in adults, and the lack of long-term randomised controlled-trial trial (RCT) data on efficacy and safety data in paediatric populations at present, weight loss expectations from anti-obesity drugs need to be viewed realistically.

In 2006, the Committee for Medicinal Products for Human Use (CHMP) of the EMA gave guidance on the development of weight control products (double-blind randomised controlled trial) for use in adults. In 2008, the CHMP outlined an addendum to give guidance on development of weight control products for paediatric populations (EMA, 2008). In general, clinical trials with anti-obesity drugs should be at least 1 year in duration (long-term) in both adults and young people. It also recommended that the observation phase after discontinuation of drug therapy should last at least 6 months. Table 1.6 presents the CHMP of EMA guidance on the development of new anti-obesity drugs in adults and paediatric population (EMA 2007). At the commencement of research for this thesis in 2007, three anti-obesity drugs were approved for obesity treatment in adults in UK clinical practice: orlistat, rimonabant, and sibutramine. Their prescribing patterns are described in Chapter 4. The details of individual anti-obesity drugs, their classes, pharmacology and indications of use will be given in the following sections.

Table 1.5: National Institute for Health and Clinical Excellence criteria for use of orlistat and sibutramine in children and adolescents (2006)*

• Drug treatment is not generally recommended for children younger than 12 years • In children younger than 12 years, drug treatment may be used only in exceptional circumstances, if severe life-threatening co-morbidities (such as sleep apnoea or raised intracranial pressure) are presented. Prescribing should be started and monitored only in specialist paediatric settings • In children aged ≥12 years, treatment with orlistat or sibutramine is recommended only if physical co-morbidities (such as orthopaedic problems or sleep apnoea) or severe psychological co-morbidities are present. Treatment should be started in a specialist paediatric setting, by multidisciplinary teams with experience of prescribing in this age group • Orlistat or sibutramine should be prescribed for obesity in children only by a multidisciplinary team with expertise in: -drug monitoring -psychological support -behavioural interventions -interventions to increase physical activity -interventions to improve diet • Orlistat and sibutramine should be prescribed for young people only if the prescriber is willing to submit data to the proposed national registry on the use of these drugs in young people • After drug treatment has been started in specialist care, it may be continued in primary care if local circumstance and/or licensing allow • If orlistat or sibutramine is prescribed for children, a 6- to 12-month trial is recommended, with regular review to assess effectiveness, adverse effects and adherence

*21st January 2010, the European Medicines Agency (EMA) announced the withdrawn of sibutramine due to the cardiovascular risks outweigh its benefits.

Table 1.6: The Committee for Medicinal Products for Human Use (CHMP) guidance on the development of weight control product in adult and paediatric population

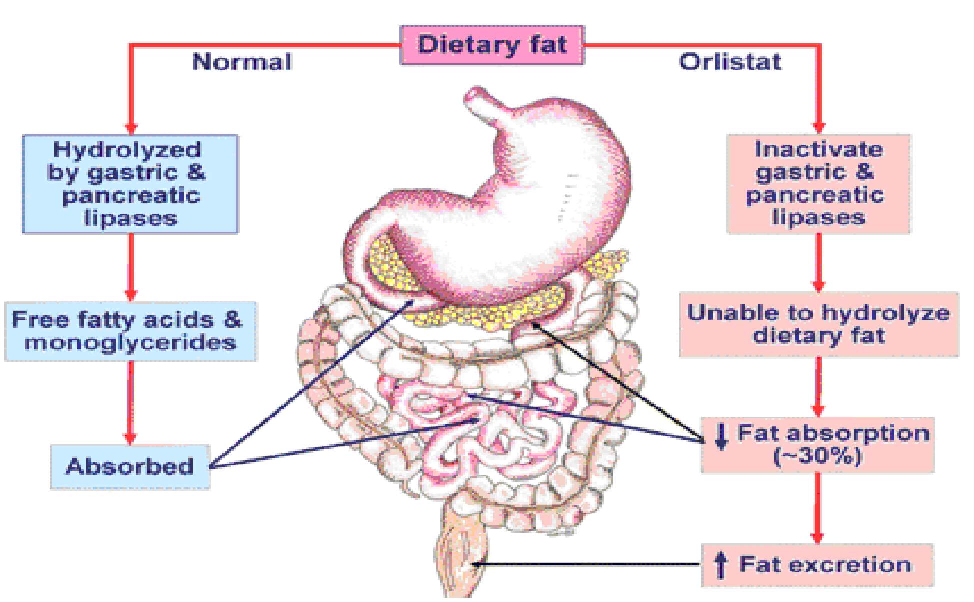
Adult • Primary endpoints for efficacy assessment: 10% of weight loss from baseline weight • The secondary efficacy variables include quality of life parameters, biochemical parameters of lipid and glucose metabolism, blood pressure, cardiac function, and sleep apnoea episodes • Selection of patients: -patients with BMI ≥30mg/m2 -patients with secondary effects of obesity (such as hypertension, hyperlipidaemia, diabetes, or cardiovascular disease) should be considered for inclusion if their BMI > 27mg/m^2 • Patients should all be given similar instruction on diet, and behaviour modification* • Drug interactions on anti-hypertensives and oral hypoglycaemic agents should be investigated • It is required that treatment effects to be documented for at least one year. If a trial is designed to demonstrate the effect of weight loss on morbidity and mortality it would require a longer prospective study **Paediatric population (children and adolescents)** • Two age categories to define paediatric population -Younger children: age 6 to 10 years (or puberty) for girls and 6 to 12 years (or puberty) for boys -Adolescents: age 10 (or puberty)to 18 for girls and 12(or puberty) to 18 years for boys • Primary endpoints for efficacy assessment: a change of BMI SDS • Secondary endpoints for efficacy assessment: improved glucose control, improved lipid profile, better mental health and/or quality of life, reduced use of adjunct medications etc. • It is not recommended that children aged 2 to 6 years receive pharmacological intervention, only lifestyle modification • Surgical intervention is normally restricted to adults • Selection of patients: -Patients with BMI≥ 25mg/m^2 (overweight), or patients with BMI ≥30mg/m^2 (obesity) -Patients with secondary causes of childhood obesity such as mental retardation, chromosomal problems or syndromic obesity (e.g. Prader-Willi syndrome) should be excluded from the trial; separate trials are needed for children with secondary causes of obesity -Patients who have undergone any surgical intervention for obesity management should be excluded from the trial • It is recommended that separate trials for younger children (6 years to puberty) versus adolescent children (puberty to 18 years) are carried out • The treatment phase should last at least 1 year • Safety data should be collected for at least one year

Abbreviations; BMI, body mass index; BMI SDS, body mass index standard deviation score. *Behaviour modification such as goal setting or use of rewards.

1.5.1.Orlistat

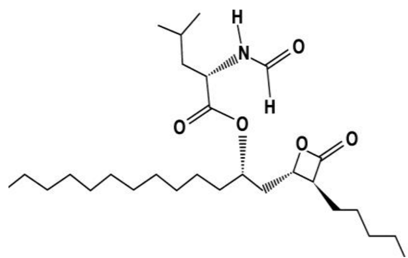
Orlistat is a hydrated derivative of endogenous lipstatin produced by *Streptomyces toxytricini* (McNeely & Benfield, 1998). It is a synthetic gastrointestinal lipase inhibitor which prevents the absorption of dietary fat by approximately 30%. It binds to pancreatic lipase and increases faecal fat excretion (Figure 1.5) (Ioannides-Demos *et al*., 2005; Padwal & Majumdar, 2007; Elangbam, 2009). Orlistat's mechanism of action is to decrease the absorption of ingested fat which decreases caloric absorption and consequently leads to weight loss. As orlistat increases fat excretion, the most frequent adverse drug reactions are gastrointestinal such as oily spotting and faecal urgency. It is recommended that patients should take a daily multivitamin supplement as orlistat may decrease the absorption of fat-soluble vitamins (vitamins A, D, E, and K) (Padwal & Majumdar 2007).

Figure 1.5: Schematic illustration of mechanism of action of orlistat (reproduced with permission from Elangbam 2009)



Orlistat was approved for obesity treatment in adults by the FDA in US and by the EMA in Europe in 1998. Table 1.7 shows detailed information about orlistat.

Table 1.7: Detailed information and licensed indications of Orlistat

Name	Orlistat
Structural Formula	
Manufacturer	Roche, GlaxoSmithKline (GSK)
Mechanism	Blocks fat absorption in the gut
Year of license	1999
Formulation	Xenical® 120mg capsules (Roche) Alli® 60mg capsules (GSK) Alli® 27mg chewable tables (GSK)
Dose	Adults: over 18 years, 120mg (up to maximal 360mg daily)
Indications from SPC	Adults: in conjunction with a mildly hypocaloric diet for obese patients with a body mass index (BMI) ≥ 30 kg/m^2 or overweight patients with BMI >28 kg/m^2 with associated risk factors. Children: there is no relevant indication for use of Xenical® in children. To use in children over 12 years, it should be initiated by specialist only [unlicensed use]
Indications from BNF-C	Initiated by specialist Children aged 12-18 years: 120 mg once daily; continue treatment beyond 12 weeks only under specialist recommendation. Vitamin supplementation (especially of vitamin D) may be considered if there is a concern about deficiency of fat-soluble vitamins.
Adverse drug reactions	Gastrointestinal adverse reactions (e.g. oily spotting, faecal urgency).

Abbreviations: SPC, Summary Product Characteristics; BNF-C, British National Formulary for Children.

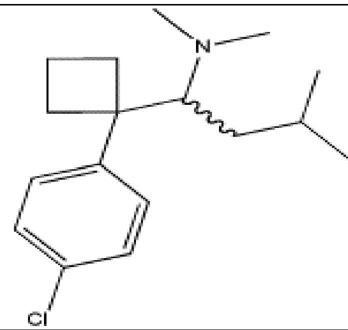
Although orlistat when licensed in 1999, was not initially licensed for use in children and adolescents, the FDA approved it for obese young people aged $\geq$ 12 in the US in 2003 (FDA, 2003). In the UK, orlistat is approved at a dose of 120 mg three times daily with meals for obesity treatment in adults aged over 18 years. As discussed (Table 1.5), in 2006 NICE recommended that orlistat may be prescribed for children aged 12 and under with life-threatening co-morbidities. According to BNF-C (2011), orlistat can only be initiated by a specialist if patients are aged 12-18 years and should be closely monitored if treatment continues for more than 12 weeks. There is limited evidence on the efficacy and tolerability of orlistat in young people since most clinical trials excluded patients younger than 18 years old (Ioannides-Demos *et al*., 2006). At the beginning of the study period in 1999, the effect of orlistat in children had not been studied (SPC 1999). Therefore, orlistat is not approved for use in obese/overweight children in the UK at present.

In 2006, the FDA approved orlistat as an over-the-counter (OTC) product at a lower dose of 60mg in US (Alli®, GlaxoSmithKline) (FDA, 2007). Subsequently, the EMA granted approval to GSK to sell 60mg and 27mg of orlistat (Alli®) as over-the-counter (OTC) products throughout Europe in 2007 (EMA, 2007). Despite the new formulation, Alli® is only licensed for obesity treatment in adults; the safety and efficacy of use in children aged under 18 years, has not been established (*Orlistat* SPC 2012).

1.5.2.Sibutramine

Sibutramine is a centrally acting appetite suppressant which was originally developed as an antidepressant. It acts by inhibiting the re-uptake of norephinephrine and serotonin (5 hydroxytryptamine; 5-HT) in the central nervous system which leads to a sense of satiety. Sibutramine also has a moderate effect on energy expenditure by stimulating thermogenesis, these effects are essential to anti-obesity actions (McNeely & Goa, 1998; Finer, 2002). Sibutramine was initially approved by the FDA for long-term (1 year) weight loss in adults in 1997 and in Europe in 2000. Detailed information on sibutramine is presented in Table 1.8.

Table 1.8: Detailed information and licensed indications of Sibutramine*

Name	Sibutramine
Structural Formula	
Manufacturer	Abbott Laboratories
Mechanism	To inhibit the re-uptake of serotonin and noradrenaline from hypothalamic neurones. A centrally acting appetite suppressant.
Year of license	2000
Formulation	Reductil®: 10mg capsule
Dose	Initially 10mg daily in the morning, increased if weight loss less than 2kg after 4 weeks to 15mg daily. Period for treatment 1 year.
Indications from SPC	Adults: obese patients with a body mass index (BMI) ≥ 30 kg/m^2 (and no associated co-morbidity) or patients with BMI >27 kg/m^2 with associated risk factors such as type 2 diabetes or hypercholesterolaemia. It is not licensed for use longer than 1 year. Children and adolescents under 18 years and elderly over 65 years not recommended.
Indications from BNF-C	BNF-C (2009): sibutramine may be chosen for patients who cannot control their eating. BNF-C (2012): No information for sibutramine use in children
Adverse drug reactions	Constipation, anorexia, dry mouth, insomnia, tachycardia, palpitation, arrhythmias, hypertension; rarely blurred vision.

Abbreviations: SPC, Summary Product Characteristics; BNF-C, British National Formulary for Children. *information from SPC were recommended before the withdrawal of sibutramine in 2010.

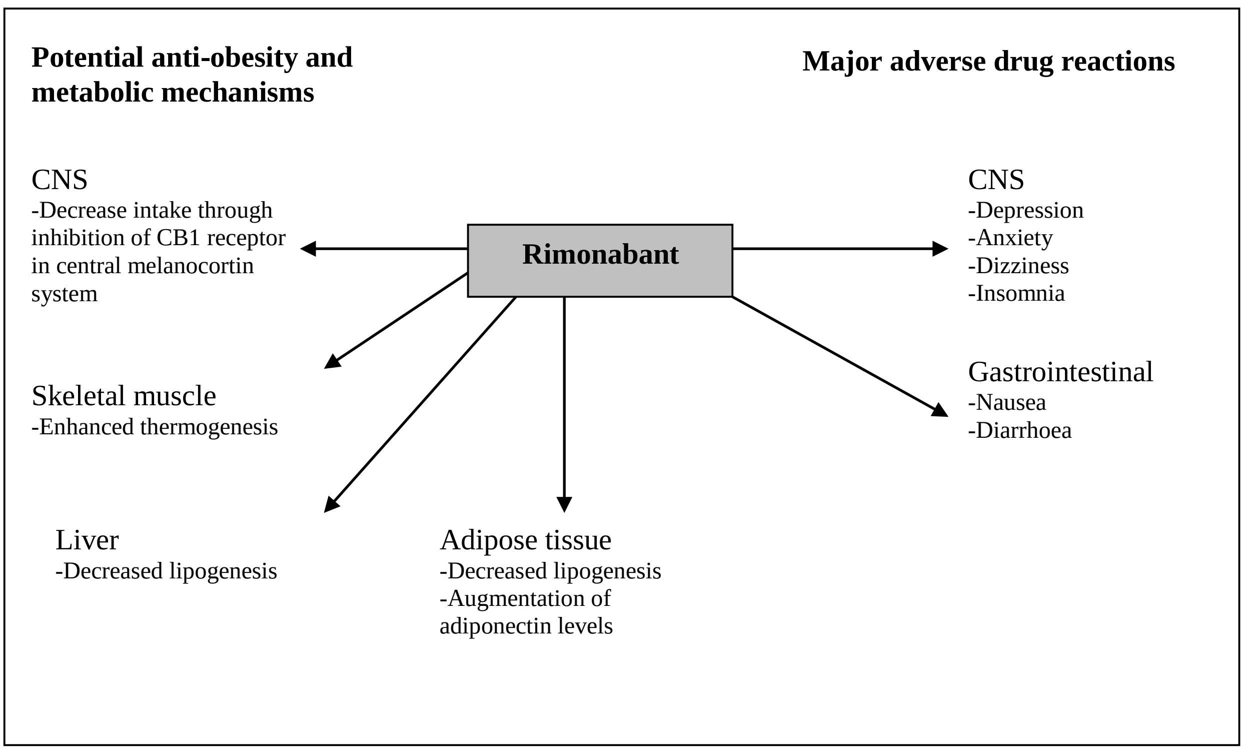
In the US, the FDA approved sibutramine for use in patients aged ≥16 years (Barlow, 2007). Although NICE guidelines (2006) suggested that sibutramine could be used for children aged ≥12 years with life-threatening co-morbidities, this drug was not licensed for use in children and adolescents for obesity treatment in the UK. In January 2010, the EMA recommended withdrawal of sibutramine from all markets in the European Union (EU). The decision was based on data from the SCOUT trial (Sibutramine Cardiovascular Outcome Trial) funded by the manufacturer, Abbott Laboratories.

The SCOUT trial was a multi-centre, double-blind, placebo-controlled randomised trial to investigate the risk of developing cardiovascular events in overweight/obese patients aged ≥55 years. Unlike other clinical trials, patients with high risk conditions (e.g. pre-existing cardiovascular diseases were eligible for the SCOUT trial (James, 2005). A total of 9,804 patients were included, of which 4,906 patients received sibutramine and 4,898 received placebo. The primary outcomes were to investigate the first occurrence of nonfatal myocardial infarction, nonfatal stroke, and resuscitation after a cardiac arrest, or cardiovascular death in both the sibutramine group and the placebo group. Despite the sibutramine group losing more weight than the placebo group, the risk of a primary outcome event was significantly increased (16%) in the sibutramine group compared with the placebo group, with overall incidences of 11.4% and 10.0% in the two groups, respectively (James *et al*., 2010). Following a review of this trial, the EMA concluded that the benefits of sibutramine did not outweigh its risks and that it should be suspended in Europe (EMA, 2010). Since the withdrawal of sibutramine, there is only one anti-obesity drug (orlistat) approved for the management of weight loss in obese or overweight adults in Europe.

1.5.3. Rimonabant

Rimonabant is a selective endocannabinoid receptor blocker, acting to inhibit the action of central and peripheral cannabinoid (CB)-1 receptors (Figure 1.6). Rimonabant modulates several peripheral signals such as ghrelin, leptin (peptides affect food intake when given peripherally) in rodents, which improve lipid and glucose metabolism and regulate food intake and energy balance (Boyd & Fremming, 2005; Henness *et al*., 2006). The most commonly reported adverse drug reactions are nausea, dizziness, diarrhoea and insomnia (Henness *et al*., 2006). Rimonabant was initially developed to treat obesity and smoking-cessation. However, development for smoking-cessation was discontinued in the US (Padwal & Majumdar, 2007). It was approved for anti-obesity treatment by the EMA in the EU in 2006 but the FDA did not grant approval for use in the US.

Figure 1.6: Rimonabant potential anti-obesity actions, metabolic and major side effects (adapted from Padwal & Majumdar 2007)



The Rimonabant in Obesity (RIO) programme included four phase III double-blind randomised controlled trials: RIO-North America (Pi-Sunyer *et al*., 2006), RIO-Europe (Van Gaal *et al*., 2005), RIO-Diabetes (Scheen *et al*., 2006), and RIO-Lipids (Despres *et al*., 2005) which were conducted to compare the efficacy of rimonabant 5mg or 20mg daily with placebo, in 6,635 overweight and/or obese patients. Table 1.9 presents the weight change from baseline after 1 year (12 months) treatment in the four RIO studies. It appears there was minimal efficacy on weight reduction with 5mg dose of rimonabant compared with the results of the 20mg dose in the four studies. The RIO-North America study also included the results of a second year of follow-up of patients who received rimonabant treatment in the first 1 year and were re-randomised to either placebo or continued to receive rimonabant (Pi-Sunyer *et al*., 2006). In the RIO-Diabetes trial, HbA1c levels improved significantly compared to placebo rimonabant (Scheen *et al*., 2006). In the RIO-Europe and RIO-North America studies, LDL cholesterol and blood pressure either did not change or were slightly reduced in rimonabant-treated patients (Pi-Sunyer *et al*., 2006; Van Gaal *et al*., 2005).

In the RIO programme, patients who withdrew from the study due to side effects, most reported mood disorders. However, the majority of the patients did not withdraw due to side effects. Also, patients who received 20 mg rimonabant were reported to have had more adverse reactions of nausea, vomiting, diarrhoea, headache, dizziness, and anxiety than the lower dose group and the placebo group. The authors stated that in the RIO-Diabetes trial, no serious adverse events linked to psychiatric disorders were recorded in rimonabant-treated patients. However, patients with severe mental illness were not included in the RIO programme, so their estimates of psychiatric adverse reactions associated with rimonabant treatment maybe conservative.

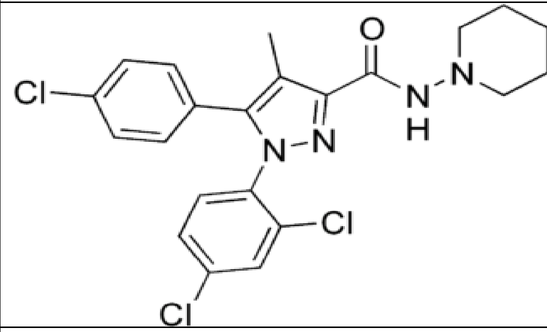
Table 1.9: One year results from four Rimonabant in Obesity (RIO) programme (Van Gaal *et al*., 2005; Despres *et al*., 2005; Pi-Sunyer *et al*., 2006; Scheen *et al*., 2006)

Study	Study population*	Study period	Study design	Weight (kg) change from baseline†				
				Placebo	5mg	*P* value (5mg rimonabant vs placebo)	20mg	*P* value (20mg rimonabant vs placebo)
RIO-North America§	3,045 overweight or obese patients in North America (US, and Canada)	August 2001-April 2004	Rimonabant 20mg daily (n=1222) vs placebo (n=607) Rimonabant 5mg daily (n=1216) vs placebo (n=607)	NA	-1.3	<0.001	-4.7	<0.001
RIO-Europe	1507 overweight or obese patients in Europe	October 2001-June 2004	Rimonabant 20mg daily (n=599) vs placebo (n=305) Rimonabant 5mg daily (n=603) vs placebo (n=305)	-3.6	-4.8	0.042	-8.6	<0.001
RIO-Lipids‡	1036 overweight or obese patients with untreated dyslipidaemia and without diabetes. Patients were from 67 centres in 8 countries	September 2001-November 2003	Rimonabant 20mg daily (n=346) vs placebo (n=342) Rimonabant 5mg daily (n=345) vs placebo (n=342)	-1.5	-3.1	<0.001	-6.9	<0.001
RIO-Diabetes	1047 overweight or obese patients with type 2 diabetes. Patients were from 159 centres in 11 countries (Europe, North America, and South America)	October 2001-May 2004	Rimonabant 20mg daily (n=339) vs placebo (n=348) Rimonabant 5mg daily (n=358) vs placebo (n=348)	-1.4	-2.3	0.01	-5.3	<0.0001

Abbreviation: NA, not available. *Study population: obese was defined as patients with body mass index (BMI) ≥30kg/m^2 and overweight as patients with BMI >27kg/m^2. ‡RIO-Lipids study included patients with BMI from 27 to 40 kg/m^2. §RIO-North America: results were reported from placebo-subtracted changes from baseline body weight. †Weight change from baseline was taken from 1 year results; intention-to-treat (ITT) approached was used and last-observation-carried-forward method was applied for missing data.

Table 1.10 presents detailed information on rimonabant. Rimonabant was not approved for use in young people aged <18 years (*Rimonabant* SPC 2008). In October 2008, the EMA's CHMP decided to withdraw rimonabant from the EU as post-marketing data and new data from on-going clinical trials had shown that serious psychiatric disorders were reported at a higher frequency than at the time of the initial assessment (EMA, 2008).

Table 1.10: Detailed information and licensed indications of Rimonabant*

Name	Rimonabant
Structural Formula	
Manufacturer	Sanofi-Aventis
Mechanism	Cannabinoid receptor-1 blocker
Year of license	2006
Formulation	Acomplia®: 20mg tablet
Dose	Adult over 18 years: 20mg daily
Indications from SPC	Adults: obese patients with a body mass index (BMI) ≥ 30 kg/m^2 or patients with BMI > 27 kg/m^2 in the presence of other risk factors such as type 2 diabetes or dyslipidaemia.
Indications from BNF-C	BNF-C: No information for rimonabant use in children
Adverse drug reactions	Depression: patients and carers should be informed of the risk of depression and advised to stop treatment and seek medical attention if symptoms occur. Nausea, vomiting, diarrhoea, dry mouth, anorexia, depression, anxiety, nervousness, sleep disorders

Abbreviations: SPC, Summary Product Characteristics; BNF-C, British National Formulary for Children. *information from SPC were recommended before the withdrawn of rimonabant in 2008.

1.5.4.New drugs potentially for obesity treatment

As discussed (see Table 1.4.), there are FDA-approved appetite suppressants for short-term obesity treatment in adults in the US such as diethylpropion and phentermine. These drugs are structurally related to amphetamines and pose a risk of addiction (Bray, 2007). These appetite suppressants are not approved for obesity treatment in Europe. In addition to the development of new drug therapies (e.g. topiramate/phentermine, bupropion/naltrexone, lorcaserin) for obesity treatment, there are several marketed drugs that have been considered for weight loss, including selective serotonin reuptake inhibitors (SSRIs) e.g. fluoxetine), antiepileptic drugs (e.g. topiramate, zonisamide), and the anti-diabetic drug (metformin). Despite the lack of long-term RCTs' data to support their use for obesity treatment, these drugs have been prescribed to obese patients in clinical practice (Ioannides-Demos *et al*., 2005; Bray, 2007; Wald & Uli, 2009). Of these drugs, metformin is considered the best drug for weight loss for patients with type 2 diabetes (Hundal & Inzucchi, 2003).

Studies have shown that metformin is also effective as an anti-obesity drug, aiding moderate weight loss in obese paediatric patients, and is commonly prescribed by doctors in clinics (Clarson *et al*., 2009; Wald & Uli 2009; Wilson *et al*., 2010; Rogovik *et al*., 2010). A systematic review that investigated five randomized controlled trials (RCTs) in children and adolescents aged $\leq$ 19 years without diabetes, showed that metformin significantly reduced BMI by 1.41 kg/m^2 (95%CI 0.83 to 2.02) over 6 months treatment (Park *et al*., 2009). Although metformin has shown a moderate effect on weight loss in children and adolescents in the short-term, there is a lack of long-term efficacy and safety studies to demonstrate its benefit on weight reduction in young people. Furthermore, metformin is only licensed for the treatment of type 2 diabetes in adults and children over the age of 10. Its use for obesity treatment has not been approved for either adults or children in the UK nor in other parts of Europe.

1.6.Summary

The treatment of obesity in young people presents a substantial challenge for health care professionals. The childhood obesity epidemic is currently one of the foremost health priorities in the UK. Despite limited evidence on the use of anti-obesity drugs in children and adolescents, these drugs are being prescribed in clinical practice. Therefore, there is a need to understand not only the efficacy and safety of these drugs but also their utilisation and prescribing patterns in obese young people. Investigation of the appropriateness of prescribing and the outcomes of pharmacological treatment in obese young people would enable clinicians to identify gaps between the evidence and clinical practice.

1.7.Scope of the thesis

The epidemic of childhood obesity is one of the common health problems affecting children in the UK. Obesity and its related conditions (e.g. diabetes, cardiovascular diseases) in childhood can persist in some patients into adolescence and adulthood. Obesity can be treated using various modes of therapy from lifestyle modification, behaviour support, or psychological intervention to the use of anti-obesity drugs.   Despite comprehensive national guidance on obesity management for children and adolescents in primary care (NICE 2006; SIGN, 2010) and secondary care (OSCA, 2012), studies reporting the use of anti-obesity drugs have been conducted in other countries with no information on their use in the UK. Data from other countries may not be extrapolated to UK practice due to differences in approaches to obesity treatment and the health care systems of various countries. Information on anti-obesity drug use in young people is therefore essential to establish patterns of prescribing in UK clinical practice.

In January 2011, the Paediatric Research in Obesity Multi-model Intervention and Service Evaluation (PROMISE) programme was launched. This programme compromises five studies and aims to improve the care and experiences of obese children and adolescents in the UK. PROMISE is led by Professor Russell Viner at University College London (UCL) Institute of Child Health (ICH) with funding from the National Institute of Health Research (NIHR). The studies of this thesis were conducted in collaboration with the PROMISE programme in particular, pharmacological interventions for obesity treatment.

Chapter 3 of this thesis describes the systematic review conducted to investigate the efficacy and adverse drug reactions from published randomised controlled trials regarding the use of anti-obesity drugs in children and adolescents. The statistical technique of meta-analysis, was employed to determine the pooled estimated treatment effects of these drugs. This information provided an understanding of the treatment effects of these drugs on weight reduction and reported adverse reactions in young people (Viner *et al*., 2010).

Chapter 4 discusses the pharmacoepidemiological methods used to investigate anti-obesity drug prescribing in children and adolescents in primary care clinical databases: the General Practice Research Database (GPRD), and IMS Disease Analyzer (IMS DA). Initially in section 4.1, the prescribing trends of anti-obesity drugs were investigated and treatment duration of these drugs was also examined (Viner *et al*., 2009). Due to the withdrawal of rimonabant and sibutramine, the use of metformin for obesity treatment may increase its popularity. Therefore, section 4.2 of Chapter 4 provides detailed information on metformin utilisation and prescribing trends in young people (Hsia *et al*., 2012).

Chapter 5 describes patterns of prescribing in the primary care setting. As suggested in the NICE guideline anti-obesity drug use should be initiated by a specialist in secondary care. There is currently no data on drug prescribing for obesity treatment from secondary care in the UK. In Chapter 5, a systematic review and meta-analysis was undertaken to investigate metformin efficacy on weight loss in non-diabetic obese children and adolescents from RCTs. Following this systematic review and meta-analysis, a prospective cohort study was conducted to investigate drug use for obesity treatment in young people at a regional secondary care sector, is reported. Initially, drug prescribing patterns for obesity treatment were investigated. This information was useful for understanding the prescribing practice for obesity treatment in secondary care. A study was subsequently conducted to assess the effect of metformin treatment on weight reduction (BMI, BMI SDS, weight) in this study population at six months of treatment.

To date, there is very little research to assess pharmacological intervention in childhood obesity management in primary care and secondary settings in the UK. It is difficult to extrapolate clinicians' experiences toward anti-obesity prescribing to obese young people from previous studies which were conducted outside UK. A national questionnaire survey was conducted to evaluate clinicians' experiences and their attitudes in prescribing anti-obesity drug to obese children and adolescents in primary care and secondary care in the UK.

Chapter 2 describes the aims and objectives of this thesis in more detail.

Chapter 2 Aim and Objectives

The overall aim of this thesis was to investigate anti-obesity drug prescribing in children and adolescents in both primary care and secondary care in the UK. Rimonabant and sibutramine were withdrawn from the market in 2008 and 2010, respectively, after the start of the work for this thesis. Therefore, data on the prescribing patterns of these drugs have been included in this thesis. To achieve this aim, three main research questions were proposed:

1) What is the evidence in the literature from RCTs concerning the efficacy and adverse drug reactions of anti-obesity drugs used in children and adolescents?
2) How are anti-obesity drug prescribed for children and adolescents in primary care in the UK?
3) What are the anti-obesity drug prescribing patterns for young people in secondary care in the UK?

To answer these questions, the following research projects were undertaken.

2.1.Systematic review and meta-analysis of RCTs of anti-obesity drugs in children and adolescents (Chapter 3)

In 2006, the recommendations from the National Institute for Health and Clinical Excellence (NICE) guidance on anti-obesity drug use in young people were based on a small number of randomised controlled trials (RCTs). There is a need for current evidence to support anti-obesity drug use in children and adolescents.

2.1.1.Aim

To systematically evaluate information from randomised controlled trials for anti-obesity drug use in young people.

2.1.2. Objective

To conduct a systematic review and meta-analysis of randomised controlled trials to investigate the efficacy and safety of anti-obesity drugs (orlistat, sibutramine, rimonabant) used in children and adolescents aged between 0 and 18 years.

2.2. Anti-obesity drug prescribing patterns to young people in primary care in the UK (Chapter 4)

The epidemic of childhood obesity is well-documented in the UK and globally. However, prior to 2007 there were few data on the use of anti-obesity drugs (orlistat, sibutramine, rimonabant) in young people in primary care in the UK. Two drug utilisation studies were conducted to investigate anti-obesity drug prescribing patterns in children and adolescents in UK primary care. In the UK, general practitioners (GPs) manage their patients' medical records electronically. These electronic records are a valuable source of data for medical research. Due to the withdrawal of rimonabant in 2008 and sibutramine in 2010, the popularity of the use of metformin for obesity treatment in clinical practice, may have increased. Therefore, the prescribing trend for metformin and the indications for its use in primary care were also examined.

2.2.1. Aims

1) To investigate anti-obesity drug (orlistat, sibutramine, rimonabant) prescribing patterns and duration of use in children and adolescents aged 18 or younger in general practices in the UK.
2) To examine the prescribing trend and indications for metformin prescribing to young people in general practices.

2.2.2. Objectives

1) To investigate annual, age- and sex-specific trends in prescribing anti-obesity drugs (orlistat, sibutramine, rimonabant) in children and adolescents aged 0-18 years between January 1999 and December 2006.
2) To determine the duration of anti-obesity drug use in children and adolescents using Kaplan-Meier survival analysis.
3) To investigate annual, age- and sex-specific metformin prescribing trends in children and adolescents between January 2000 and December 2010.

4) To examine indications for metformin prescribing in children and adolescents in general practices.

2.3. Anti-obesity drug prescribing patterns to obese young people in the secondary care (Chapter 5)

Due to the withdrawal of sibutramine in January 2010, currently orlistat is the only drug recommended by NICE guideline for obesity treatment. Several potential marketed drugs have been used for obesity treatment in clinical practice in the UK (Chapter 1, section 5). Of these metformin is suggested as the best drug of choice, because obese patients are likely to have metabolic syndromes. To date, there is limited evidence on the effect of metformin treatment on weight loss in obese young people either from RCTs or from clinical practice. A systematic review and meta-analysis of published RCTs was undertaken to investigate the efficacy of metformin treatment on weight loss in this population. Following this review a prospective cohort study was conducted in a paediatric weight management clinic at University College London Hospital (UCLH). Data were collected from January 2007 to December 2010 to investigate anti-obesity drug prescribing patterns. Subsequently an observational cohort study was conducted to determine the effect of metformin treatment on weight loss in patients who received this drug for obesity treatment in this paediatric clinic.

2.3.1. Aims

1) To investigate the efficacy of metformin treatment on weight loss in obese young people from RCTs.

2) To investigate pharmacological interventions in obese young people at University College London Hospital (UCLH) paediatric weight management clinic.

2.3.2. Objectives

1) To conduct a systematic review and meta-analysis to investigate metformin efficacy from published RCTs in non-diabetic children and adolescents aged 0-18 years.

2) To describe anti-obesity drug prescribing patterns for patients aged 10-18 years attending a weight management clinic at UCLH, between January 2007 and December 2010.

3) To determine the effect of metformin treatment on weight loss at 6 months of treatment for patients attending a weight management clinic at UCLH aged 10-18years.

2.4. Anti-obesity drug prescribing patterns to young people in primary care and secondary care: a national questionnaire survey study (Chapter 6)

Several studies have been carried out to assess health practitioners' behaviour towards childhood obesity management in clinical practice. These studies primarily evaluated practitioners' attitudes toward childhood obesity management in general. None of these studies specifically evaluated practitioners' experiences in pharmacological intervention to manage childhood obesity in their clinical practice. Furthermore most of these studies were conducted outside the UK. To date, there has been very little research to evaluate health practitioners' attitudes and experiences on prescribing anti-obesity drugs to obese children and adolescents across different clinical settings in the UK. A questionnaire survey was conducted to assess clinicians' attitudes and experiences on prescribing anti-obesity drug to young people for obesity treatment in primary care.

2.4.1. Aims and objectives:

The aim of this study was to survey clinicians about their anti-obesity drug prescribing practice to obese young people in their clinical practice via questionnaires. There were four specific objectives:

1) To investigate GP experiences on prescribing anti-obesity drugs to young people
2) To investigate GP knowledge and skills on prescribing anti-obesity drugs
3) To investigate the reasons for discontinuing anti-obesity drug treatment.
4) To identify key elements for future prescribing guidance or intervention to support prescribing of anti-obesity drugs to young people in both primary care and secondary care.

Chapter 3 Systematic review and meta-analysis of randomised controlled trials on anti-obesity drugs

3.1.Introduction

As discussed earlier, there has been an increase of childhood obesity worldwide during past decades. Although attention has focused mainly on lifestyle modification interventions, a role for the use of anti-obesity drugs in the treatment of children and adolescents has been identified (Freemark, 2007). Detailed information on anti-obesity drugs have been described previously (Chapter 1.5). However, the NICE recommendation of prescribing anti-obesity drug for children and adolescents was based on a limited evidence base, with a small number of randomised controlled trials for each drug. There is a need for current evidence to support the use of these drugs in young people (Freemark, 2007).

Two systematic reviews were identified on obesity treatment in children and adolescents (McGovern *et al*., 2008; Oude *et al*., 2009). McGovern *et al*. (2008) conducted a systematic review on randomised trials of nonsurgical interventions (diet, physical activity, and pharmacological agents) in overweight children and adolescents aged 2-18 years to investigate the efficacy of obesity treatment. These authors reported on the overall efficacy of three pharmacological interventions (orlistat, sibutramine, metformin) regardless of the different length of follow-up of the studies. The pooled estimate from the meta-analysis in the review showed that orlistat reduced BMI by 0.7 kg/m^2 (95% CI 0.3 to 1.2) and the reduction of BMI for sibutramine treatment was 2.4 kg/m^2 (95% CI 1.8 to 3.1). Use of metformin showed a small non-significant BMI reduction of 0.17 kg/m^2 (95% CI -0.62 to 0.28). A Cochrane review by Oude *et al.* (2009) investigated lifestyle interventions (diet, physical activity and/or behavioural therapy interventions), drug therapy (orlistat, sibutramine, metformin, rimonabant) and surgical interventions in obese children aged less than 18 years. In this Cochrane review, the authors included drug trials that had at least up to 3 months drug therapy and 6 months follow up period. In these two reviews, of pharmacotherapy use in paediatric populations, adverse drug reactions (ADRs) associated with the anti-obesity drug treatment were not investigated. Therefore, a systematic review and meta-analysis of randomized controlled trials investigating the efficacy and safety of the use of anti-obesity drugs in children and adolescents was conducted. In this systematic review, three anti-obesity drugs approved at the time in the UK were included: orlistat, sibutramine, and rimonabant.

3.2.Aim and objective

The overall aim of this review was to evaluate the efficacy and safety of anti-obesity drugs used in children and adolescents. This was achieved by conducting a systematic review and meta-analysis of randomised controlled trials of anti-obesity drugs. Specific objectives included:

1) To assess the efficacy of anti-obesity drugs (orlistat, sibutramine, rimonabant) used in children and adolescents aged between 0 to 18 years.

2) To evaluate adverse drug reactions (ADRs) related to anti-obesity drug treatment in children and adolescents aged between 0 to 18 years.

3.3.Systematic review of randomised controlled trials

There has been an increasing amount of scientific information about health care. In order to integrate this large amount of information into practice, published studies need to be reviewed and the evidence for a specific topic summarised for health care professionals (Egger *et al*., 2001). Traditionally, reviews of medical literature summarise the studies and examine the heterogeneity of them, and then report them descriptively in the form of "narrative review" (Petticrew, 2003). Although narrative review has been widely used in medical research, it has been criticised for its high risk of selection bias. In addition, studies may use a variety of methods and this may often lead to contradictory findings in a narrative review (Cook *et al*., 1997). To ensure the results of the literature review are less biased, systematic review and meta-analysis have gained popularity amongst health care professionals in recent years.

Systematic reviews use explicit methods to search evidence and to summarise the literature systematically. Systematic reviews are defined as "*scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their subjects. They synthesise the results of multiple primary investigations by using strategies that limit bias and random error*" (Mulrow, 1987; Cook *et al*., 1995). A systematic review may, or may not, include a meta-analysis (Egger *et al*., 2001). Meta-analysis is a statistical method of summarising data from individual studies and produces a pooled estimate of intervention effect (Egger *et al*., 2001). A detailed discussion of meta-analysis is presented in the subsequent section.

The term *systematic review* was first used by Archie Cochrane, a British physician and epidemiologist, known for his influential book, *Effectiveness and Efficiency: Random Reflections on Health Services*, published in 1972. Cochrane identified a lack of access for people who wanted to have reliable evidence in health care. He also stressed the importance of collating evidence from RCTs as these can provide more reliable information than evidence from other sources. Although his ideas have received enormous support, applying his approach in research has been very slow (Chalmers, 1993; Chalmers *et al*., 2002). Systematic reviews were not widely used until the 1990s. In 1992, in response to Cochrane's call for "*systematic, up-to-date reviews of all relevant RCTs of health care*", the first Cochrane centre was established in Oxford to support the National Health Service (NHS) (Chalmers, 1993). The following year, the Cochrane Collaboration was set up to provide healthcare professionals, policy makers and patients with well-documented evidence through systematic reviews of the effect of health care interventions. In addition, the Cochrane Collaboration is able to provide evidence at international level (http://www.cochrane.org/).

Cook and colleagues (1997) tabulated the differences between systematic reviews and traditional narrative reviews (Table 3.1). A systematic review is generally driven by a specific research question. A well-formulated research question can help reviewers to make decisions about which studies are relevant and should be included and which are not relevant and therefore should be excluded, during the review process (Greenhalgh, 1997).

Table 3.1: Summary of the differences between narrative reviews and systematic reviews (adapted from Cook *et al*., 1997)

Feature	Narrative review	Systematic review
Question	Often broad in scope	Often a focused clinical question
Sources and search	Not usually specified, potentially biased	Comprehensive sources and explicit search strategy
Selection	Not usually specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal
Synthesis	Often a qualitative summary	Quantitative summary*
Inference	Sometimes evidence-based	Usually evidence-based

*A quantitative summary which includes a statistical synthesis is a meta-analysis.

Traditional narrative review is often conducted to cover a broad range of issues related to a specific topic (Cook *et al*., 1997). The advantage of a narrative review is that it provides a broad perspective on a specific topic and it may also be useful for background reading. However, a narrative review does not normally describe how reviewers selected and assessed the studies during the review process. The absence of explicit methods may cause methodological flaws, and may bias the reviewers' conclusion and could result in inappropriate recommendations (Murlow, 1987; Akobeng, 2005). As narrative reviews are not conducted via a pre-planned method it is sometimes difficult to replicate the findings (Feldstein, 2005; Egger *et al*., 2001). In addition, it can be difficult to identify important information required for guiding improvements to treatment, from narrative reviews which sometimes will cause a delay in implementing changes (Greenhalgh, 1997). The Cochrane Collaboration logo is a striking example to demonstrate the unnecessary delay in implementing new therapy. Detailed explanation of the Cochrane Collaboration logo is discussed in the next section (see section 3.5). However when conducting systematic reviews, all existing published literature should be examined and analysed in a structured way which assists rational decision making for clinicians, researchers, and policy makers. Systematic reviews have now often replaced traditional narrative reviews in medical research.

As a result of the success of the Cochrane Collaboration programme, the number of published systematic reviews has increased substantially in the past decade, it has now become an important part of epidemiological research (Mulrow, 1994; Blettner *et al*., 1999; Egger *et al*., 2001). Systematic reviews have been classified as similar to observational studies by utilising available evidence for research (Egger *et al*., 2001). To conduct a high quality scientific, systematic review, comprehensive steps must be followed which are outlined in Table 3.2.

Table 3.2: Steps for conducting systematic review with or without meta-analysis (Egger *et al*., 2001)

1. Formulate review question
2. Define inclusion and exclusion criteria
• Participants
• Interventions and comparisons
• Outcomes
• Study designs and methodological quality
3. Locate studies
Develop search strategy considering the following sources:
• The Cochrane Controlled Trials Register (CCTR)
• Electronic databases and trials registers not covered by CCTR
• Checking of reference lists
• Hand searching of key journals
• Personal communication with experts in the field
4. Select studies
• Have eligibility checked by more than one observer
• Develop strategy to resolve disagreements
• Keep log of excluded studies, with reasons for exclusions
5. Assess study quality
• Consider assessment by more than one observer
• Use simple checklists rather than quality scales
• Always assess concealment of treatment allocation, blinding and handling of patient attrition
• Consider blinding of observers to authors, institutions and journals
6. Extract data
• Design and pilot data extraction form
• Consider data extraction by more than one observer
• Consider blinding of observers to authors, institutions and journals
7. Analyse and present results*
• Tabulate results from individuals studies
• Examine forest plot
• Explore possible sources of heterogeneity
• Consider meta-analysis of all trials or subgroups of trials
• Perform sensitivity analyses
• Make list of excluded studies available to interested readers
8. Interpret results
• Consider limitations, including publication and related biases
• Consider strength of evidence
• Consider applicability
• Consider numbers-needed-to-treat to benefit / harm
• Consider economic implications
• Consider implications for future research

*This step describes when systematic review and meta-analysis are conducted in the review.

Data sources that could be searched for relevant articles also need to be considered before a systematic review is undertaken. Greenhalgh (1997) provided a list of possible data sources that could be included in a systematic review (Table 3.3). It is also recommended that the references from identified articles are searched, which may not have been included in the initial search. If data are not available in published RCT studies, review authors should consider contacting study authors for information (Higgins & Green, 2009).

Table 3.3: Data sources for systematic reviews (Greenhalgh, 1997)

1	MEDLINE database
2	Cochrane controlled clinical trials register
3	Other medical and paramedical databases (e.g. PsycINFO)
4	Foreign language literature
5	Grey literature (e.g. thesis, internal reports, non-peer reviewed journal, pharmaceutical industry files)
6	References (and references of references, etc.) listed in primary source
7	Other unpublished sources known to experts in the field (e.g. personal communication)
8	Raw data from published trials (e.g. personal communication)

3.4.Meta-analysis of randomised controlled trials

The term meta-analysis was first introduced by Glass in 1976 to emphasise the need for better summary of research results. Glass defined meta-analysis as "*the statistical analysis of a large collection of analysis results from individual studies for the purpose of integration of the findings*" (Glass, 1976). There are two types of meta-analysis: meta-analysis of randomised controlled trials and meta-analysis of epidemiological studies such as observational studies (Egger *et al*., 2001). Meta-analysis of observational studies is beyond the scope of this thesis, so there is no further discussion of these techniques and issues.

Meta-analysis is a powerful statistical tool; by bringing together samples from individual studies the sample size is increased as well as the precision of the estimates of intervention effects (Sutton *et al*., 2000). As discussed, meta-analysis is a part of the systematic review process but it may not be necessary to include it. The Cochrane Statistical Methods Group provides several reasons for not including a meta-analysis in a review; these are listed below (Higgins & Green, 2009):

1. If studies are clinically diverse then a meta-analysis may be meaningless, and genuine differences in effects may be obscured. Furthermore, it is important not to combine outcomes that are too diverse. Decisions concerning what should and should not be combined are inevitably subjective, and are not amenable to statistical solutions but require discussion and clinical judgement.
2. If bias is present in each (or some) of the individual studies, meta-analysis will simply compound the errors, and produce wrong results that may be interpreted as having more credibility.
3. Meta-analysis in the presence of serious publication and/or reporting biases are likely to produce an inappropriate summary.

In general, there is a two-stage process of conducting meta-analysis. The first stage of meta-analysis is to calculate the effect size; such as the treatment effect between two interventions, with 95% confidence intervals (CI) for each of the individual studies, the 'effect measurement(s)' used depend on the outcome data available. There are two types of effect: dichotomous data (binary) and continuous data (Sutton *et al.,* 2000; Akobeng, 2005; Higgins & Green, 2009). The three most commonly used effect measurements for dichotomous outcomes data are: 1) risk ratio (RR) (also called relative risk); 2) the odds ratio (OR); 3) the risk difference (RD). *Risk* is the number of patients with an event (outcome) divided by the total number of patients. Odds describe the ratio of the probability that an event (outcome) occurred to the probability that it did not occur (Higgins & Green, 2009). For continuous data, the most commonly used calculation in meta-analysis for effect measurement, is mean difference (MD). The MD is a summary statistic to measure the difference between the mean value in the two groups (experimental group and control group) in a clinical trial (Higgins & Green, 2009).

The second stage of meta-analysis is to estimate a summary (pooled) of the treatment effect. The treatment effect is calculated as a weighted average of the intervention effects estimated in each individual study (Sutton *et al*., 2000; Higgins & Green, 2009). The graph used to display the results of the weighted results in meta-analysis is called a "forest plot". The first forest plot of a meta-analysis was produced by Lewis and Ellis in 1982. In general, the smaller studies will produce less precise estimate with wider confidence intervals (Lewis & Clarke, 2001). There are two approaches that can be used to investigate overall treatment effect; fixed effect model and random effect model. The fixed effect model assumes that treatment effect sizes are the same in all studies. This approach can only reflect overall treatment variations within trials, not between trials. In contrast to the fixed model, the random effect model assumes treatment effect sizes are different and that variations exist within and between studies (Sutton *et al*., 2000). Therefore, the random effect model is favoured over the fixed model in routine use.

It is essential to assess the consistency of effects across studies in meta-analysis, as there maybe variability amongst studies. The variability in meta-analysis is called "heterogeneity". Several causes of heterogeneity have been suggested; 1) due to chance, 2) the scale used to measure the treatment effect, 3) patient-level covariates which can be further investigated if individual patient data are available, 4) characteristics of study design, and 5) unexplainable (if none of the above account for it) (Sutton *et al*., 2000). It is important to examine to what extent the results of studies are consistent. Therefore, it is common to test for heterogeneity to investigate the consistency of findings when combining studies (Higgins & Green, 2009).

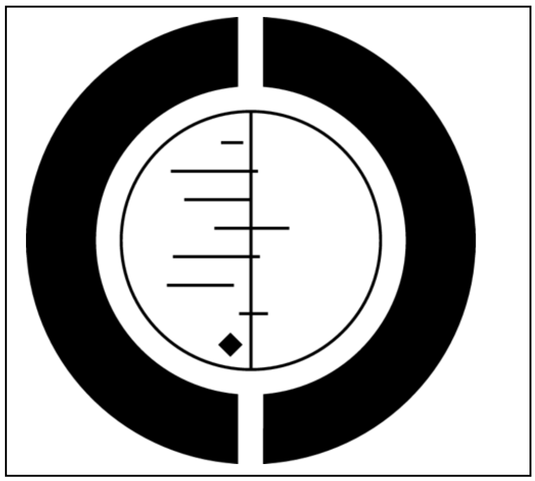
The usual measurement of heterogeneity in meta-analysis is Cochrane's Q. The Cochrane's Q is the chi-square statistic test, which is calculated as the weighted sum of square differences between individual study effects and pooled effects across studies (Higgins *et al*., 2003). Another measurement to test heterogeneity is I^2 value to quantify inconsistency across studies. I^2 value is calculated as: (Q-df)/Q x 100%, where df is degrees of freedom (Higgins, 2003). The Cochrane review group has suggested a rough guideline to interpret I^2 value as below (Higgins & Green, 2009):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If I^2 value greater than 30%, the P value from chi-square test and/or confidence interval for I^2 value are also indicators to show the extent of heterogeneity. A commonly used approach to quantity the magnitude of variance between studies in a random-effect model is to measure tau-square (τ^2 or Tau^2). The value of τ^2 takes into account the variance both within studies and between studies.

As mentioned, the Cochrane Collaboration logo is an example to demonstrate the advantage of conducting systematic review and meta-analysis. The Cochrane Collaboration logo is a representation of a systematic review of data from 7 RCTs conducted between 1972 and 1982 (Figure 3.1).

Figure 3.1: Cochrane Collaboration logo (reproduced with permission from Cochrane Library)



The review was performed to investigate corticosteroids given to women expected to give birth prematurely. The graphical test in the middle of the logo is called a "forest plot". Each horizontal line represents the result of an individual trial, and the length of line represents the confidence intervals (the wider the line, the more uncertain the result). The vertical line indicates the position around which the horizontal lines would cluster if the treatments compared in the trials had similar effects. The diamond at the bottom is the combined results (pooled estimated treatment effect). If the position of diamond is on the left of the vertical line, this indicates that the treatment in the trials is beneficial (Cochrane website: http://www.cochrane.org/about-us/history/our-logo).

The results from this systematic review showed that there was about a 30-50% reduction of death for the babies born to women who had received corticosteroids (Chalmers, 1993). Unfortunately, this review was not performed until 1989. If these RCTs had been systematically reviewed earlier, the benefit of corticosteroid therapy would have been recognised as early as the 1980s, and it may have saved many premature babies' lives. There are similar examples to show the inadequacy of traditional narrative reviews resulting in delays in adopting beneficial therapy (Feldstein, 2005).

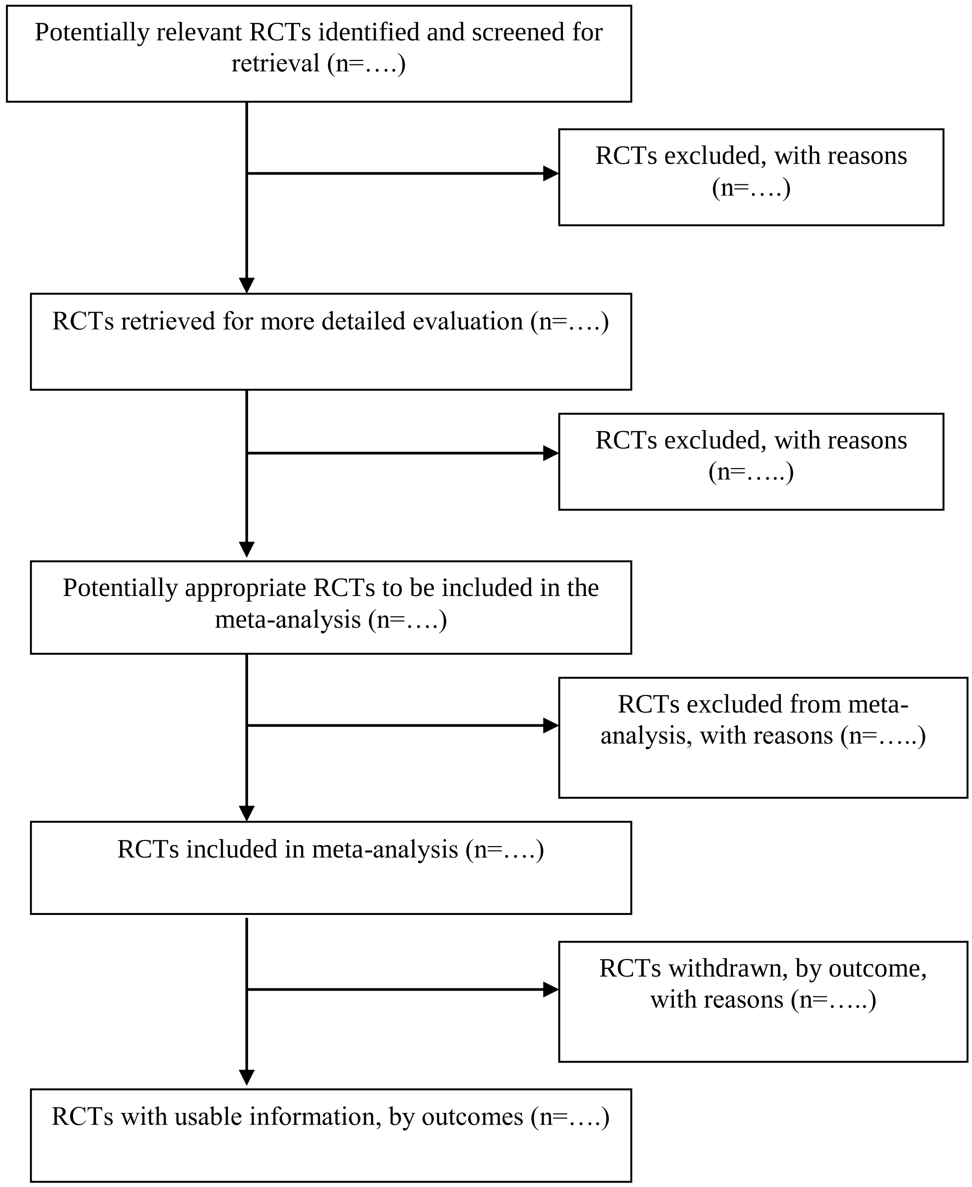
Despite the obvious advantages of systematic review and meta-analysis, there are potential problems that need to be addressed. The findings from a systematic review only be as reliable only as the included studies' quality. To combine poorly-performed studies may sometimes produce misleading results. Moher and colleagues (1998) randomly selected 11 meta-analyses which included 127 RCTs on interventions for digestive diseases, mental health, pregnancy and childbirth. They found a statistically significant 30-50% exaggeration of treatment efficacy when lower quality studies were included. The similar finding was reported by Schulz *et al*., (1995), they examined 33 meta-analyses that involved 250 clinical trials from the Cochrane Pregnancy and Childbirth Database. Studies with inadequate allocation concealment overestimated the treatment efficacy by 30-40% compared to studies that had adequate allocation concealment. It is essential to assess the methodological quality in the review process as poor-quality studies may produce results that are biased and imprecise.

Another potential problem for systematic reviews is publication bias. The publication bias has been long recognised in medical research (Chalmers, 1993). Studies with positive results are more likely to be published therefore these studies are more easily identified for a systematic review. To include only published studies is likely to overestimate the intervention efficacy consequently this may lead to a biased estimate of treatment effect (Sutton *et al*., 2000; Egger *et al*., 2001). The statistical method that has been developed to minimise publication bias is the test for funnel plot asymmetry. This test is used to examine whether the association between the estimated treatment effect and the study size (e.g. standard error of treatment effect) is greater than might be expected to occur by chance (Higgins & Green, 2009). The Cochrane Collaboration suggested that a funnel plot asymmetry test can only be conducted if there are at least 10 studies included in the meta-analysis. This is because the power will be too low to detect the bias when a small number of studies are included. There have been several initiatives to improve the methodological quality of reporting systematic reviews and meta-analysis (Egger *et al*., 2001). In 1996, the QUOROM (*QU*ality *O*f *R*eporting *O*f *M*eta-analysis) statement was developed and published in 1999. The QUOROM statement was developed by a group of epidemiologists, clinicians, statisticians, and researchers who are interested in meta-analyses and who conducted meta-analyses in the UK and North America (Moher *et al*., 1999). The QUOROM statement was mainly developed for reporting meta-analysis of RCTs. The statement included a checklist and a flow diagram. The checklist is organised into 21 headings and subheadings, and provides review authors with a standard way to present their reports. The flow diagram gives information about the number of RCTs identified, included, excluded, and the reasons for their exclusion. The QUOROM statement checklist is presented in Table 3.4 and the QUOROM flowchart in Figure 3.2.

Table 3.4: QUOROM statement checklist: the quality of reports for meta-analysis of randomised controlled trials (adapted from Moher *et al*., 1999)

Heading	Subheading	Descriptor
Title		Identify the report as a meta-analysis (or systematic review) of RCTs
Abstract		Use a structured format Describe:
	Objective	The clinical question explicitly
	Data Source	The databases (i.e. list) and other information sources
	Review methods	The selection criteria (i.e. population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (i.e. point estimates and confidence intervals); and subgroup analyses
	Conclusion	The main results
Introduction		The explicit clinical problem, biological rational for the intervention, and rationale for review
Methods		
	Searching	The information sources, in detail (e.g. databases, registers, personal files, expert information, hand-searching), and any restrictions (years considered, publication status, language of publication).
	Section	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design)
	Validity assessment	The criteria and process used (e.g. masked conditions, quality assessment, and their findings)
	Data abstraction	The process or processes used (e.g. completed independently, in duplicate)
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, and how clinical heterogeneity was assessed.
	Quantitative data synthesis	The principal measures of effect (e.g. relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessment; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias.
Results	Trial flow	Provide a meta-analysis profile summarising trial flow (see figure)
	Study characteristics	Present descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up period)
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome): present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (e.g. 2x2 tables of counts, means and SDs, proportions)
Discussion		Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in the light of the totality of available evidence; describe potential biases in the review process (e.g. publication bias); and suggest a future research agenda

Figure 3.2: The QUOROM statement flow diagram: improving the quality of reports of meta-analysis of randomised controlled trials (adapted from Moher *et al*., 1999)



The QUOROM statement is a useful guideline to help researchers to undertake systematic reviews and meta-analysis, in particular for RCT studies however, there is an increasing use of systematic reviews to summarise evidence from other types of research (e.g. observational studies). In 2005, a group of 29 review authors, methodologists and clinicians developed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement (Liberati *et al*., 2009). PRISMA, which is an evolution of the QUOROM guideline, consists of a 27-item checklist for the reporting of meta-analyses, covering title, abstract, methods, results, discussion and funding. Together with a four-phase flow diagram to guide researchers through the different stages of systematic reviews in different phases. The advantage of the PRISMA statement is that it can also be used to report systematic reviews and meta-analysis for studies other than RCTs. As this project commenced prior to the publication of the PRISMA statement, the QUOROM statement was used in this systematic review.

3.5. Methods

3.5.1. Inclusion and exclusion criteria

All randomised placebo-controlled clinical trials (RCTs) investigating the efficacy and safety of the three anti-obesity drugs, orlistat, sibutramine, rimonabant, in children and adolescents aged under 19 years were included. All clinical trials included, needed to provide at least 6 months data as it is more important to evaluate the longer term effects of treatment. Quasi-randomised, open label crossover trials, open labelled non-blinded randomised trials, and studies published only in abstract form were excluded from the review. Since a range of definitions of childhood obesity exist, any trials which used an established definition of overweight or obesity (BMI $\geq 85^{th}$, 95^{th} or 98^{th} percentile; BMI > International Obesity Taskforce definition) were included in this review.

3.5.2. Outcome measures

To be included in this review, studies had to have reported a change in the body mass index (BMI) as the primary outcome measure or to have presented a baseline and a post-treatment measurement, as these data can be used to calculate a change in BMI from baseline, if not reported within the study. The secondary outcome measures were adverse drug reactions (ADRs) related to anti-obesity drug treatment.

3.5.3. Search methods for identification of studies

The following databases were searched from January 1996 to January 2008 for clinical trials investigating anti-obesity drugs and body weight reduction in children and adolescents aged under 19: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). Additionally, a number of trial register websites were searched for corroborative evidence: the metaRegister of Controlled Trials (www.controlled-trials.com), WHO clinical trial register (http://www.who.int/ctrp/en/), and the government Clinical trials register (http://www.clinicaltrials.gov/). Search strategies and search terms for individual electronic databases are presented in Appendix 1 (MEDLINE), Appendix 2 (EMBASE), and Appendix 3 (CENTRAL). A further hand search was also carried out to examine the reference lists of the identified studies. Studies were not excluded on the basis of language.

3.5.4. Data Extraction and Quality Assessment

The electronic database searches were performed by two reviewers; Yingfen Hsia, and Tania Tomsic- currently a clinical pharmacist at General Hospital Novo Mesto in Slovenia. The electronic searches of all databases were performed independently. Once the searches had been completed, the two reviewers screened all the included abstracts separately. This initial review was to check whether these studies met the eligibility criteria. If studies clearly did not meet the inclusion criteria they were rejected on initial review. The full text of studies marked for potential inclusion were then obtained electronically or in paper copy, and assessed again for inclusion in the review. Any disagreement between the two reviewers, over which papers should be included, was resolved by discussion with Professor Russell Viner[1] to reach consensus. The included studies, deemed to meet the inclusion criteria, were then appraised by both reviewers.

A standardised form was used to record all the details of the papers reviewed (Egger *et al.*, 2001). The standard form included study design, blinding status, trial duration, mean age of participants, gender, and numbers of participants in the treatment and placebo groups, interventions, and the assessment of intention-to-treat (ITT). The QUORUM (Quality of Reporting of Meta-analyses) guideline was used for reporting the review (Moher, 1999).

[1] Professor Russell Viner is a consultant and director of Adolescent Medicine, University of College London Hospital and Great Ormond Street Hospital.

3.6.Statistical Analysis

The primary outcome was expressed as a change in raw BMI (kg/m^2) rather than in BMI standard deviation score (SDS), as use of BMI SDS masks significant loss of body mass in the very obese during adolescence. We calculated weighted mean differences for continuous outcomes (e.g. BMI) and risk differences for dichotomous outcomes, at the end of the study follow-up period. A random effects model was used for the meta-analysis of this review.

The primary outcome analysis (BMI) was based upon intention to treat data from the completion of the randomised trial, prior to any cross-over or open label extension. However, data on secondary outcomes and adverse drug reactions were taken from the same trial end-point as the BMI data, using the highest quality data reported in each trial; whether the ITT population, a subset of the ITT population, or completers (patients who completed the treatment during the clinical trial period). Where standard deviations were not reported, these were calculated from standard errors, t values or p values that related to the differences between means in the two groups.

The DerSimonian and Laird Q test (the random effect) was performed to assess the degree of heterogeneity between studies, and the I^2 statistic was used to describe the percentage of total variation across studies due to heterogeneity. Due to the small number of studies included, we were unable to assess publication bias by inspection of funnel plot asymmetry. Secondary outcomes (e.g. fasting lipids, glucose or insulin) were included in the meta-analysis if each outcome was reported in ≥2 studies for each drug. All analyses in this review were performed using RevMan 5.0.16 (Review Manager 2011). RevMan is a software programme that can be used to prepare study protocols and summarise findings in tables and/or graphs. It can also perform meta-analysis of included studies and present the results graphically. This software can be downloaded free of charge for preparing a Cochrane review or for academic purposes.

3.7. Results

3.7.1. Studies identified from searching and screening

The extensive search identified 101 studies (Figure 3.3). The titles and abstracts of these 101 studies were screened to ascertain if the studies were relevant; 85 studies did not meet the inclusion criteria. The most common reasons for exclusion of studies were the participants' age, >20 years, it was a review article or it had a different primary outcome. The full articles of the remaining 16 studies were retrieved (Table 3.5). Two of the 16 studies were identified as sub-group analyses and excluded (Budd *et al*., 2007; Daniels *et al*., 2007) the remaining 14 studies met the criteria for inclusion (Table 3.6).

3.7.2. Appraisal of the clinical trial studies

Details of the remaining 14 studies are shown in Table 3.6. Of the 6 studies of orlistat; 4 were excluded,3 were open-label uncontrolled studies (McDuffie *et al*., 2002; Norgen *et al*., 2003; McDuffie *et al*., 2004), and one (Ozkan *et al*., 2004) was an open-label non-blinded randomised controlled trial. Eight of the appraised studies were for sibutramine; 4 of which were excluded from the meta-analysis, 2 were open-label studies without a control (placebo) group (Reisler *et al*., 2006; Violante-Ortiz *et al*., 2005), 1 randomised controlled trial had a study duration of only 3 months (Van Mil *et al*., 2007), and 1 randomised controlled trial excluded subjects with primary or nutritional obesity (Danielsson *et al*., 2007). Two studies of orlistat, 4 studies of sibutramine, and no study of rimonabant were identified as eligible for meta-analysis.

3.7.3. Study subjects and co-interventions

Subjects across all the trials included in the meta-analysis had similar demographic profiles; the majority of the participants were aged 12-18 years, their mean BMI was between 30kg/m^2 and 40kg/m^2, and they were predominantly white or Hispanic. In each trial, subjects with secondary causes of obesity were excluded, as were those with diabetes mellitus. All trials included a standardised low fat low energy diet and encouragement to exercise, with a variable element of behavioural modification in some trials.

Figure 3.3: QUOROM statement flowchart for the randomised controlled trials of anti-obesity drug use in children and adolescents: from January 1996 to January 2008

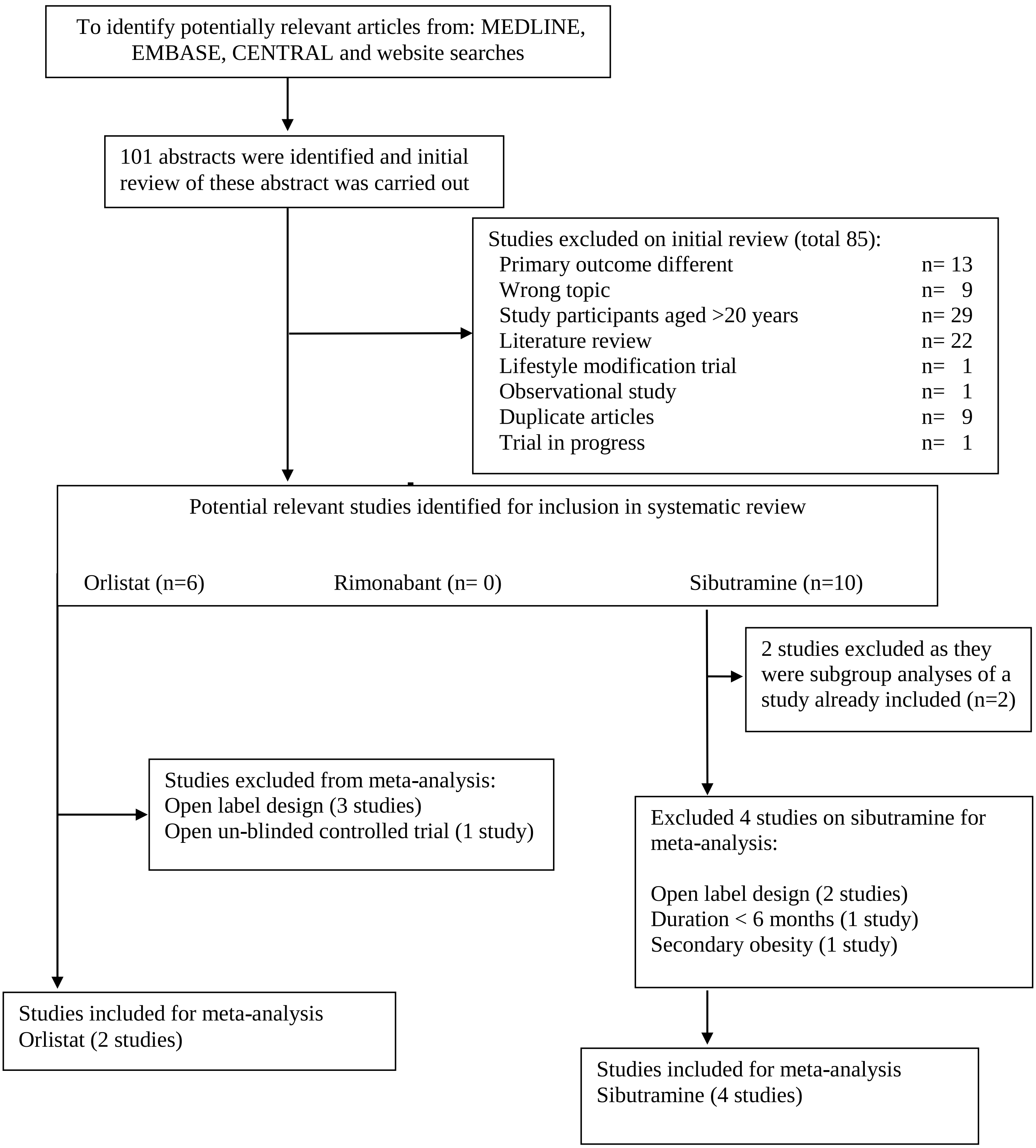


Table 3.5: Studies included for full text review

Orlistat studies	Author	Study title
	McDuffie *et al.* (2002)	Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions
	Norgren *et al.* (2003)	Orlistat treatment in obese prepubertal children: a pilot study
	Ozkan *et al.* (2004)	Addition of orlistat to conventional treatment in adolescents with severe obesity.
	McDuffie *et al*. (2004)	Efficacy of orlistat as an adjunct to behavioural treatment in overweight African American and Caucasian adolescents with obesity-related co-morbid conditions
	Chanoine *et al*. (2005)	Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial
	Maahs *et al*. (2006)	Randomized, double-blind, placebo-controlled trial of orlistat for weight loss in adolescents
Sibutramine studies	**Author**	**Study title**
	Berkowitz *et al*. (2003)	Behaviour therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial.
	Godoy-Matos *et al*. (2005)	Treatment of obese adolescents with sibutramine: a randomized, double-blind, controlled study
	Violante-Ortiz *et al*., (2005)	Use of sibutramine in obese Hispanic adolescents
	Garcia-Morales *et al*. (2006)	Use of sibutramine in obese Mexican adolescents: a 6-month, randomized, double-blind, placebo-controlled, parallel-group trial
	Berkowitz *et al.* (2006)	Effects of sibutramine treatment in obese adolescents: a randomized trial
	Reisler *et al.* (2006)	Sibutramine as an adjuvant therapy in adolescents suffering from morbid obesity
	Budd *et al*. (2007)	Weight loss in obese African American and Caucasian adolescents: secondary analysis of a randomized clinical trial of behavioural therapy plus sibutramine
	Van Mil *et al.* (2007)	The effect of sibutramine on energy expenditure and body composition in obese adolescents.
	Daniels *et al.* (2007)	Cardiovascular effects of sibutramine in the treatment of obese adolescents: results of a randomized, double-blind, placebo-controlled study
	Danielsson *et al*. (2007)	Impact sibutramine therapy in children with hypothalamic obesity or obesity with aggravating syndromes

Table 3.6: Appraised trials of sibutramine and orlistat for weight reduction in children and adolescents

Study	Location	Design	Duration	Age (yrs)	Sample case: placebo	BMI (SD) before treatment	Co-intervention	Dose	Ethnic group	Meta-analysis
Orlistat RCT										
Chanoine *et al*. 2005	US, Canada	RCT	54 wk	12-16	357: 182	*Case*: 35.7±4.2 *Placebo:* 35.4±4.1	Diet; behavioural modification; exercise counselling	Orlistat 120 mg t.i.d	White: 141 Black: 25 Other: 15	Yes
Maahs *et al*. 2006	US	RCT	6 mo	14-18	20: 20	*Case:* 39.2±1.2 *Placebo:* 41.7±2.6	Dietary counselling; exercise counselling	Orlistat 120 mg t.i.d	White	Yes
Orlistat Open-label trial										
McDuffie *et al*. 2002	US	OL	3 mo	12-17	20	44.1±12.6	Diet; behavioural programme	Orlistat 120 mg t.i.d	White: 10 African American: 10	No
Norgen *et al*. 2003	Sweden	OL	12 mo	7-12	11	33.3	Diet	Orlistat 120 mg t.i.d or q.i.d	Scandinavian	No
McDuffie *et al*. 2004	US	OL	6 mo	12-17	20	White: 36.2±1.2 African American: 50.3±1.3	Diet; behavioural programme	Orlistat 120 mg t.i.d	Caucasian: 10 African American: 10	No
Ozkan *et al*. 2004	Turkey	OC	5-15 mo	10-16	22:20	*Case*: 32.5 *Placebo*: 31.2	20% reduction in daily calories based on age and gender; increased activity level	Orlistat 120 mg t.i.d	White	No
Sibutramine RCT										
Berkowitz *et al*. 2003	US	RCT followed by OL	*Phase 1*:6 mo RCT *Phase 2*: 6 mo OL	13-17	43:39	37.8±3.8	Behavioural protocol; dietary counselling, encouraged exercise	*Phase 1* 15 mg sibutramine daily *Phase 2* All received sibutramine	White: 54.9 % Black: 41.5% Others: 3.6%	Yes
Godoy-Matos *et al.2005*	Brazil	RCT	6 mo	14-17	30:30	*Case* Female: 37.5±3.8 Male: 37.6±4.3 *Placebo* Female:35.8±4.2 Male:37.4±1.9	500 kcal/d deficit diet; dietary counselling; encouraged exercise	Sibutramine 10mg q.d	Brazilian	Yes
Berkowitz *et al*. 2006	US	RCT	12 mo	12-16	368:130	*Case:* 36.1±3.8 *Placebo:* 35.9±4.1	500 kcal/d deficit diet; behaviour protocol; encouraged exercise	mo 1-5: sibutramine 10 mg q.d.mo 6: increased to 15mg in participants who did not lose ≥ 10% BMI from baseline	White 57% Black 21% Hispanic 16%	Yes

Continue.

Study	Location	Design	Duration	Age (yrs)	Sample case: placebo	BMI (SD) before treatment	Co-intervention	Dose	Ethnic group	Meta-analysis
Sibutramine RCT										
Garcia-Morales *et al*. 2006	Mexico	RCT	6 mo	14-18	23:23	*Case:* 35.1±5.3 *Placebo:* 36.6±5.2	Dietary recommendations	Sibutramine 10 mg q.d.	Mexican	Yes
Danielsson et al., 2007	Sweden	RCT followed by OL	20wk+20 wk RCT, followed by 6 mo OL	7-20	50	Range: 2.9-9.7	Lifestyle modification	Phase 1:sibutramine 10mg q.d.; dose was tailored up to 15mg, if bw reduction <4kg within 8 wk Phase 2: sibutramine 10mg or 15 mg	Scandinavian	No
Sibutramine Open-label trial										
Van Mil *et al*. 2007	NL	RCT	3 mo	12-18	12:12	*Case:* 30.1±4.5 *Placebo:* 33.3±5.0	Dietary and exercise advice	Sibutramine 5 mg q.d.; after 2 wk the dose was increased to 10 mg q.d.	White	No
Reisler *et al*. 2006	Israel	OL	12 mo	13-18	20	40±5.6	Calorie-restricted diet; encouraged exercise	Sibutramine 10 mg q.d	White	No
Violante-Ortiz *et al*. 2005	Mexico	OL	6 mo	12-18	67	34.2±6.0	Diet, aerobic physical activity	Sibutramine 10 mg	Mexican	No

Abbreviations: NL, the Netherlands; BMI, body mass index; RCT, randomized controlled trial; OL, open-label; OC, open (un-blinded) control trial; SDS, standard deviation score; bw, body weight; t.i.d, three times a day; q.d, once a day; q.i.d, four times a day; mo – months; wk: week.

3.7.4. Methodological quality

Studies were all of similar quality based on the QUOROM checklist. All studies included an intention to treat analysis, reported eligibility criteria, and co-interventions were similar in intervention and control groups. Most studies did not describe the randomisation process nor were there comments on allocation concealment or blinding of outcome assessors. Since there was little variation in quality, a sensitivity analysis according to study quality was not performed. Secondary end points of interest were reported inconsistently, and frequently in a sub-group of patients or not in an extractable fashion.

3.8. Studies included in meta-analysis

3.8.1. Orlistat

Two studies fulfilled the criteria to be included in the meta-analysis, with a total sample size for BMI outcomes of 573 adolescents. One ran for 6 months and one for 12 months. Each used the recommended dose of orlistat, 120 mg three times daily, and participants also received behavioural, dietary and exercise counselling. Participants in both studies also received multi-vitamin supplements. Figure 3.4 shows that the pooled estimate of mean BMI change with orlistat was a reduction of 0.83 kg/m^2 (95% CI 0.47 to 1.19) compared with placebo. There was no evidence of heterogeneity. An analysis of proportions achieving 5 and 10% BMI or weight loss was not undertaken as this was reported in only 1 study.

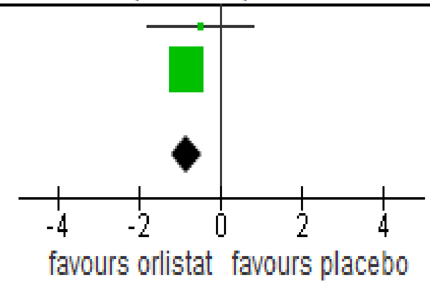
Secondary outcomes for orlistat compared with placebo are shown in Table 3.7. There were no significant differences in fasting lipids, glucose or insulin between orlistat and placebo. As waist circumference, body fat and blood pressure were each only reported in a single study, these outcomes were not included in the meta-analysis. The effect of orlistat and placebo on changes in vitamin A, D and E levels were not included in the meta-analysis as the dose of multi-vitamin used in each trial was not specified; however, both studies reported no significant difference in levels of each vitamin between groups during the trial. Sensitivity analyses for orlistat were not undertaken due to the low study numbers. Adverse reactions for orlistat compared with placebo are shown in Table 3.7. Those taking orlistat were significantly more likely to experience a range of gastrointestinal adverse reactions. It was not possible to assess the risk of specific gastrointestinal event, or study discontinuation due to gastrointestinal adverse reactions, as studies only provided the overall number of patients reported with gastrointestinal adverse reactions. The reasons for discontinuation of treatment were not clearly reported in the studies.

Figure 3.3: Mean reduction in body mass index (kg/m^2) with orlistat

	orlistat			placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Maahs 2006	-1.3	2.63	20	-0.8	1.41	20	7.5%	-0.50 [-1.81, 0.81]
Chanoine 2005	-0.55	3.11	352	0.31	1.25	181	92.5%	-0.86 [-1.23, -0.49]
Total (95% CI)			**372**			**201**	**100.0%**	**-0.83 [-1.19, -0.47]**

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 4.56 (P < 0.00001)

Mean Difference
IV, Random, 95% CI



Heterogeneity statistics: a test for differences across studies using Tau^2 (tau-squared), the chi-square test, and I^2 statistic to express the among-study variance. Percent weights were given to each study.

Table 3.7: Secondary outcomes and adverse drug reactions with orlistat

Secondary outcomes	No. of Patients*			Weighted mean difference (95%CI)
	Orlistat	Placebo	Total	
Fasting				
Triglycerides (mmol/L)	368	199	567	0.00 (-0.17, 0.18)
Cholesterol Total (mmol/L)	339	181	520	0.03 (-0.17, 0.23)
HDL (mmol/L)	339	181	520	0.00 (-0.02, 0.03)
LDL (mmol/L)	338	180	518	-0.05 (-0.11, 0.01)
Glucose (mmol/L)	298	154	452	0.02 (-0.25, 0.28)
Insulin (mU/L)	287	150	437	-0.41 (-4.83, 4.01)
GI Adverse drug reactions				
Fatty /oily stool	368	199	467	0.53 (0.27, 0.79)
Oily spotting	368	199	467	0.49 (0.00, 0.99)
Oily evacuation	368	199	467	0.51 (-0.08, 1.10)
Faecal urgency	368	199	467	0.10 (0.04, 0.16)
Flatus with discharge	368	199	467	0.17 (0.12, 0.21)
Flatulence	368	199	467	0.05 (0.01, 0.09)
Faecal incontinence	368	199	467	0.08 (0.05, 0.11)

*Number of patients in each group for whom secondary outcomes and/or adverse drug reactions were reported. Two studies were included in this analysis: Maahs *et al*. (2006) and Chanoine *et al*. (2005).

3.8.2.Sibutramine

Data from 4 RCTs were included in the meta-analysis, with a total sample size for BMI outcomes of 464 adolescents. Three studies ran for 6 months and one study for 12 months. Two studies used a dose of 10mg of sibutramine per day, 1 study used 10 mg per day for the first 6 months, increasing the dose to 15mg per day for the second 6 months if subjects had failed to lose ≥10% of initial BMI (Berkowitz *et al.*, 2006), and 1 study used a dose which increased from 5mg to 15mg over the first 7 weeks (Berkowitz *et al.*, 2003)

Figure 3.5 shows that the pooled estimate of mean change in BMI was a reduction of 2.20 kg/m^2 (95% CI: 1.57 to 2.83). The heterogeneity statistic showed a moderate heterogeneity (I^2:47%) between studies but there was no significant heterogeneity (p=0.13). Secondary outcomes for sibutramine compared with placebo are shown in Table 3.8. For sibutramine treatment, the loss of ≥5% of initial BMI was 45% and 39% for the loss of ≥10% initial BMI, and decreased waist circumference by nearly 6cm on average, compared with placebo. Sibutramine was associated with significant improvements in triglycerides and HDL-cholesterol compared with placebo (2 studies each). Data were unavailable on the effect of sibutramine on body composition e.g. fat mass loss.

3.8.3.Sensitivity analyses

Sensitivity analyses were conducted for study duration (6 or 12 months) and the use of a behaviour therapy programme (BT) as a co-intervention. A BT co-intervention was used for all study participants in two (Berkowitz *et al.*, 2003; Berkowitz *et al.*, 2006) of the four sibutramine studies. Sibutramine plus BT co-intervention produced a mean BMI reduction of 2.23 (95% CI -3.12 to -1.34) kg/m^2 compared with placebo and BT. Sibutramine without BT produced a mean BMI reduction of 2.04 (95% CI -3.50 to -0.58) kg/m^2. The intention to treat analysis (ITT) was undertaken at 6 months in 3 studies and 12 months in 1 study. Sibutramine produced a mean BMI reduction of 2.60 (95% CI -3.16 to -2.04) in the single 12 month study (Berkowitz *et al*., 2006) and 1.95 kg/m^2 (95% CI -2.81 to -1.08) in the three 6 month studies.

The 6 month analyses were repeated with the addition of an intermediate non-intention to treat data from the 6 month assessments in the single 12 month study. Mean BMI reduction across the 4 studies at 6 months was largely unchanged: -2.02kg/m^2 (95% CI -2.49 to -1.55). It was not possible to undertake a sensitivity analysis with respect to sibutramine dose.

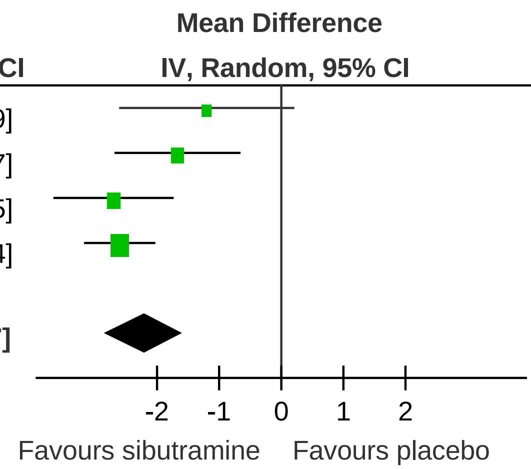
Adverse drug reactions to sibutramine compared with placebo are shown in Table 3.8. Those receiving sibutramine had higher systolic (1.4 mmHg) and diastolic (1.7 mmHg) blood pressure and heart rate (4.7 beats per minute) (4 studies each). As hypertension was not an exclusion condition in all studies, and because of variable data reports, we were unable to assess trial withdrawal due to hypertension across the studies. Those taking sibutramine were also significantly more likely to experience a dry mouth but there were no other adverse reactions.

Figure 3.4: Mean reduction in body mass index (kg/m^2) with sibutramine

	sibutramine			placebo				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
García 2006	-3.2	2.2	23	-2	2.6	23	14.9%	-1.20 [-2.59, 0.19]
Berkowitz 2003	-3.19	2.55	43	-1.52	2.05	39	22.9%	-1.67 [-2.67, -0.67]
Godoy 2005	-3.6	2.5	30	-0.9	0.9	30	24.2%	-2.70 [-3.65, -1.75]
Berkowitz 2006	-2.9	2.88	368	-0.3	2.74	130	38.0%	-2.60 [-3.16, -2.04]
Total (95% CI)			**464**			**222**	**100.0%**	**-2.20 [-2.83, -1.57]**

Heterogeneity: Tau² = 0.19; Chi² = 5.70, df = 3 (P = 0.13); I² = 47%

Test for overall effect: Z = 6.84 (P < 0.00001)



Heterogeneity statistics: a test for differences across studies using Tau^2 (tau-squared), the chi-square test, and I^2 statistic to express the among-study variance. Percentage weights were given to each study.

Table 3.8: Secondary outcomes and adverse drug reactions with sibutramine

Secondary outcomes	No. of Study	No. of Patients*			Weighted mean difference (95% CI)
		Sibutramine	Placebo	Total	
Fasting					
Waist circumference (cm)	4	375	167	542	-5.78 (-7.03, -4.52)
Triglycerides (mmol/L)	2	299	96	395	-0.31 (-0.39, -0.23)
Cholesterol Total (mmol/L)	2	46	38	84	-0.02 (-0.72, 0.69)
HDL	2	299	96	395	0.09 (0.05, 0.13)
LDL	2	46	38	84	-0.18 (-0.62, 0.25)
Glucose (mmol/L)	2	46	38	84	-0.04 (-0.08, 0.00)
Insulin (mU/L)	2	300	95	395	-4.21 (-9.79, 1.38)
Systolic blood pressure (mmHg)	4	453	205	658	1.38 (0.13, 2.63)
Diastolic blood pressure (mmHg)	4	453	205	658	1.73 (1.01, 2.46)
Heart rate (beats per minute)	4	453	205	658	4.70 (1.65, 7.76)
Adverse drug reactions					
Headache	3	419	179	589	-0.08 (-0.24, 0.08)
Dry mouth	3	419	179	589	0.06 (0.01, 0.11)
Dizziness	2	398	160	558	0.02 (-0.02, 0.06)
Abdominal pain	2	398	160	558	0.00 (-0.05, 0.06)
Constipation	2	398	160	558	0.14 (-0.12, 0.40)
Flu-like symptoms	2	398	160	558	0.01 (-0.04, 0.05)
Weight loss					**Risk difference (95% CI)**
Loss of ≥5% of initial BMI	4	377	171	548	0.45 (0.32, 0.59)
Loss of ≥10% of initial BMI	4	377	171	548	0.39 (0.31, 0.65)

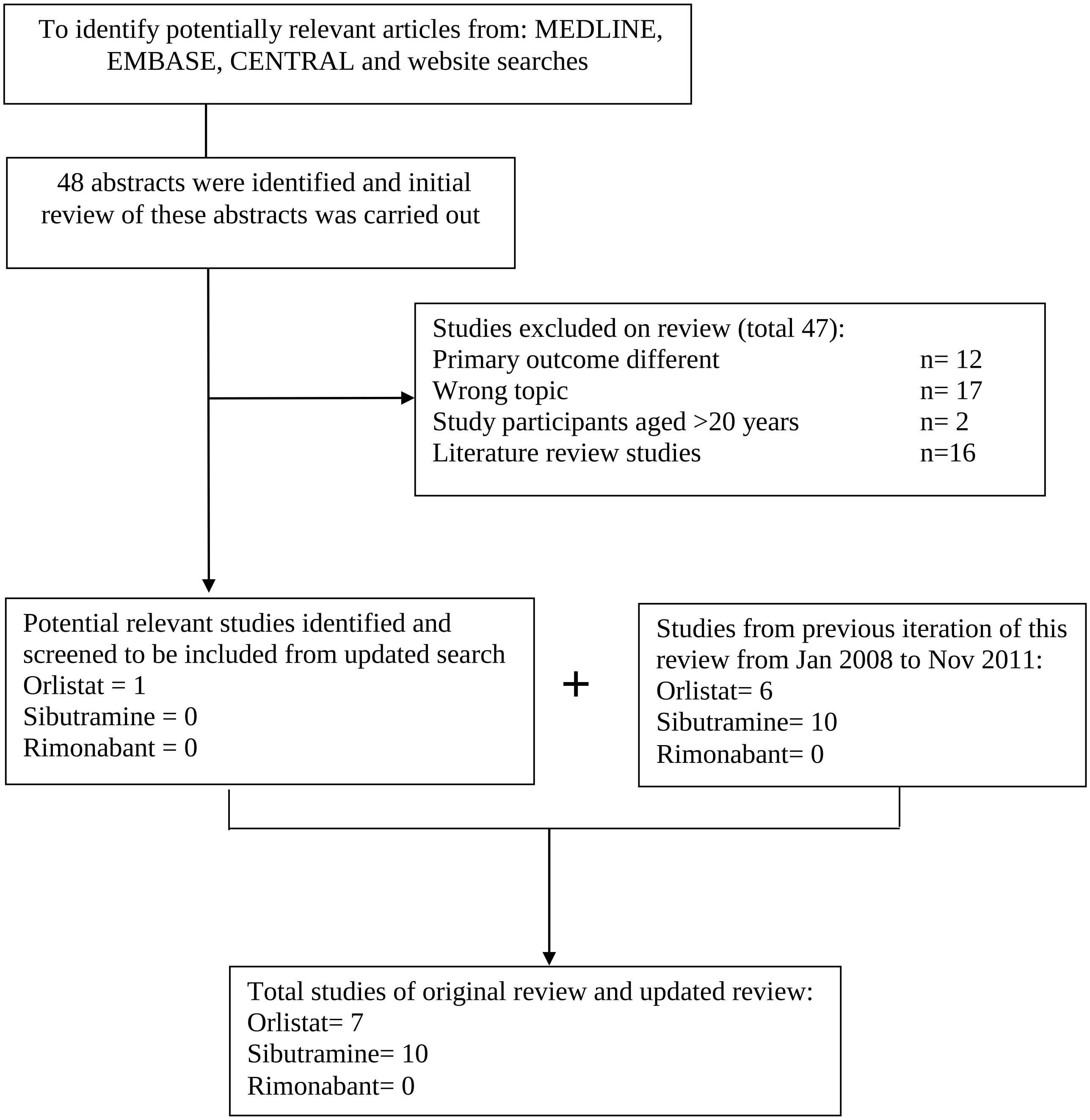
Number of patients in each group for whom secondary outcomes and/or adverse drug reactions were reported.

3.9.Updated systematic review

It is common practice for researchers to update systematic reviews after a certain period of time following completion of the original review (Moher & Tsertsvadze, 2006). As discussed, one of the advantages of systematic reviews is that it is easy to replicate the search. On 7th August 2014, an updated search was carried out using the same search strategies. The updated search results from February 2008 to August 2014, are summarised in the QUORUM flow diagram given in Figure 3.6.

The updated search identified 48 studies. Of these, 47 studies were excluded after reviewing abstracts. One study was included after the abstract had been screened (Chanoine & Richard, 2011). The full article of this study was obtained for inclusion in the final review. This included study was an additional analysis from a previous one which had already been included in our original review (Chanoine *et al*., 2005). This additional analysis was to compare the relationship between weight changes in the orlistat treated group and control group at baseline and 12 weeks after treatment, as well as metabolic markers change. As this secondary analysis of orlistat use did not meet the inclusion criteria, this study was excluded after reviewing the full article.

Figure 3.5: Flowchart for the randomised controlled trials of anti-obesity drug in children and adolescents: an updated from February 2008 to August 2014



3.10.Discussion

Meta-analysis of randomised controlled trials of anti-obesity drugs in children and adolescents with primary obesity showed that treatment with either orlistat or sibutramine resulted in a significant BMI reduction compared with placebo: 0.83 kg/m^2 for orlistat and 2.20 kg/m^2 for sibutramine. The clinical significance of such reductions will vary with the BMI distribution in different populations: the standard deviation (SD) for BMI in mid adolescence is approximately 2.7 kg/m^2 in the UK and approximately 3.5 kg/m^2 in the USA (Cole *et al*., 1995; CDC, 2009).

The effect size for orlistat was smaller and of borderline clinical significance at 0.24-0.3 SD. While orlistat had no beneficial or adverse effects on metabolic outcomes, it was associated with an approximately 50% increase in minor gastrointestinal adverse events such as oily spotting and an 8-17% increase in the absolute incidence of more major gastrointestinal events such as flatus with discharge and faecal incontinence.

For sibutramine, this is a clinically meaningful mean effect size (0.6-0.8 SD) for BMI reduction. Sibutramine also increased the absolute percentage of those achieving a ≥10% BMI loss by approximately 40%, it also reduced waist circumference by a mean of 5.8 cm compared with placebo, an effect size of approximately 1.0 SD (McCarthy *et al*., 2003) and improved HDL-cholesterol minimally. Sensitivity analyses suggested that the addition of behaviour therapy programmes to sibutramine use, minimally increased mean BMI loss (0.2 kg/m^2), and also that a longer duration of sibutramine use may increase BMI loss by approximately 0.6 kg/m^2. Adverse drug reactions with sibutramine included significant but small increases in systolic and diastolic blood pressure, heart rate, dry mouth. There was no increase in the risk of other adverse reactions.

3.11.Comparison with the literature

The findings of this review are similar to those of a recent meta-analysis of anti-obesity drug use in children and adolescents by McGovern *et al*. (2008), which reviewed drug trials as part of a wider systematic review of childhood obesity treatment. They reported a mean BMI reduction for sibutramine from 3 RCTs of 2.4 kg/m^2, similar to our finding of 2.2 kg/m^2, and a mean BMI reduction for orlistat of 0.7 kg/m^2, again similar to our finding of 0.83 kg/m^2 (McGovern *et al*., 2008). However, McGovem *et al*. this review included un-blinded studies therefore the inclusion criteria differ from our review. In addition, they also included sibutramine and orlistat as subcategories within a larger random-effects meta-analysis and did not undertake sensitivity analyses or examine secondary outcomes in detail. A recent systematic review by Oude *et al*. (2009) reported similar findings for orlistat (mean reduction of 0.76 kg/m^2). This review included only two small studies in a meta-analysis for sibutramine, reporting a mean reduction of 1.66 kg/m^2, considerably lower than our estimate. Neither of these published systematic reviews undertook a meta-analysis of adverse reactions with orlistat or sibutramine.

This review did not compare findings directly with results from adult studies as BMI loss is not directly comparable to weight loss, either in terms of absolute loss or proportions of people who lose ≥5% or ≥10% of initial weight. Weight loss was not included in this review, as BMI reduction is the goal of treatment of obesity in childhood and adolescence, growing children may lose BMI while gaining weight and BMI centiles continue to shift in later adolescence even after height growth has ceased (Viner *et al*., 2000). However, approximate comparisons can be made for older adolescents who are at or near final height.

Meta-analyses in adults have shown that weight loss from sibutramine and orlistat are limited to 3kg to 4 kg over 12 months (Rucker *et al*., 2007). In contrast, the weight loss corresponding to a loss of 2.2 kg/m^2 related to sibutramine use in 14- and 15-year old adolescents with a height on the 50th centile for their sex is approximately equivalent to a 6 kg loss for boys and girls, a relationship that holds true across the obese BMI range. The corresponding weight loss for orlistat is approximately 2.3 kg. The reasons for this are unclear. This may be an artefact of the paucity of data on adolescents and also the lack of long-term data. Alternatively, this may suggest sibutramine is more potent in suppressing appetite in adolescents, possibly due to developmental immaturity in their hypothalamic appetite control systems.

Sibutramine was found to have modest beneficial effects on triglycerides and HDL-cholesterol, similar to findings in adults (Rucker *et al*., 2007). However, we found no evidence of beneficial metabolic effects associated with orlistat use, in contrast to a meta-analysis in adults which suggested that orlistat has a small beneficial effect on LDL and total cholesterol (Rucker *et al*., 2007). The reasons for this difference are unclear but may relate to the modest BMI loss seen with orlistat in adolescents and the small number of studies included in the meta-analysis. In addition, if patient's the levels of cholesterol are not abnormal at baseline, it would not necessarily expect a reduction of weight loss. The effect of orlistat had been studied and related to the reduced absorption of triglyceride from the gut and lower portal delivery of fat to the liver. This may be a weight-independent effect such as atherosclerosis. (Suter et al., 2005).

Study quality was relatively high; attrition rates (25% for orlistat and 19% for sibutramine) were moderately high, but lower than those reported in a meta-analysis of adult trials of these drugs (30% for orlistat; 0% for sibutramine) (Rucker *et al*., 2007). However, the number of studies of each drug in adolescents is limited, and the trials had all been undertaken in secondary care settings, limiting the generalisability of the findings (see Table 3.6). We were unable to identify any published studies with a duration ≥ 12 months, so we could not examine long-term maintenance of BMI loss. Our findings apply to young people with simple or primary obesity. However, we note that our BMI effect size for sibutramine is similar to that of 0.7 SD BMI reduction reported by Danielsson *et al*. (2007) in a randomised controlled trial of sibutramine for 20 weeks in adolescents with secondary or monogenic obesity (Danielsson *et al*., 2007) which was not eligible for inclusion in our meta-analysis.

3.12. Safety

The safety profile of orlistat was similar to that noted in adults i.e. a marked increase in unpleasant and anti-social gastrointestinal experiences but there was little evidence of significant health risks. Theoretical concerns about fat-soluble vitamin deficiencies were not supported although subjects in both trials were given multi-vitamins. In contrast, sibutramine was generally well tolerated by subjects but was associated with small rises in systolic and diastolic blood pressure and resting heart rate. The magnitude of these changes is very similar to that seen in adult studies; a recent meta-analysis found that sibutramine increased adults' systolic blood pressure by 1.7 mmHg, diastolic blood pressure by 2.4 mmHg and heart rate by 4.5 beats/min (Rucker *et al.*, 2007). Even small increments in blood pressure can have an adverse impact on cardiovascular risk in the long-term, particularly in at-risk groups such as obese adolescents, who often have higher blood pressure compared with peers. Authorities note that the long-term safety of anorectic agents has not been established in children and adolescents (Freemark *et al.*, 2007). However, the clinical significance of small blood pressure increments over a short treatment period remains unclear, particularly when balanced against the beneficial cardiovascular effects of successful weight reduction.

3.13. Strengths and Limitations

A rigorous systematic review and meta-analysis was undertaken using independent reviewers adhering to the established Cochrane Collaboration methodology. In contrast to adult studies (Ruckner *et al.*, 2007), studies in the review included a range of non-white ethnic groups. However, the findings have several limitations which need to be noted. Firstly, all published studies have demonstrated efficacy of orlistat and sibutramine in BMI and body weight reduction. This suggests the possibility of publication bias; however there were too few studies for either drug to warrant the generation of funnel plots to assess publication bias. Secondly, there was a moderate but non-significant statistical heterogeneity between the studies for sibutramine BMI outcomes. This was addressed by using a random effects meta-analysis. It is likely that this heterogeneity was the result of differences in co-interventions, study duration and study population. The review included studies of differing length in the meta-analysis, as it was not possible to standardise duration due to the differing timings of the ITT analysis. The reviewers did not have access to individual patient data to investigate the cause of this heterogeneity.

Thirdly, for sibutramine, one trial was excluded from the meta-analysis as study duration was only 3 months and an ITT analysis was not performed (Van Mil *et al*., 2007). Repeating the meta-analysis for BMI, including this study, reduced the estimate of BMI reduction to -1.8 kg/m^2 (95% CI: -2.65 to -0.95). Fourthly, all included studies were conducted in specialist environments, and the generalisability of these findings to more general populations of obese adolescents is unclear. Finally, the analyses only included data that were extractable from studies, which may be a source of bias as studies may only publish secondary outcomes that differed significantly from placebo. This was the case for the largest included trial of sibutramine, Berkowitz *et al*., (2006), which only published metabolic outcomes that differed significantly between sibutramine and placebo, and the reviewers were unable to include in the analyses this study's data on secondary outcomes that were not significantly different. However, the analyses found no significant mean difference for any of these secondary outcomes in the studies that were included in the meta-analyses for these outcomes.

3.14.Conclusion

Evidence from this systematic review has shown that sibutramine together with behavioural support in obese adolescents produces a clinically meaningful reduction in BMI of 0.6-0.8 SD with raised blood pressure. In contrast, orlistat with behavioural support produces a minimal effect (0.24-0.3 SD) with frequent gastrointestinal adverse reactions which has limited utility as a weight reduction treatment in adolescents. As sibutramine was withdrawn from the EU market in 2010, a further study to assess long-term maintenance of effectiveness of orlistat treatment in young people is needed.

Chapter 4 Anti-obesity drug prescribing patterns to young people in primary care in the UK

4.1.Introduction

In the UK, patients are primarily registered with a general practitioner (GP). Although there is no accurate official figure for the population registered with a GP, it has been estimated that approximately 95% of the UK population is registered with a GP (Lawrenson *et al*., 1999). A small proportion of patients due to their circumstances, may not be registered with a GP; these include the homeless, those who choose not to register, prisoners, and members of the armed forces (Lawrenson *et al*., 1999). In the UK, the general practitioners (GPs) act as the gatekeeper for patient healthcare through the National Health System (NHS). GPs are responsible for providing primary care and for organising referrals to specialist care for their patients. When patients are seen in secondary care (e.g. hospitals), consultants or specialists will make the diagnosis and initiate treatment, and GPs will usually continue to monitor patients with chronic conditions and issue prescriptions. In recent years, most GPs have used computers to assist with the management of their clinical practices. The official survey figure has shown that over 90% of practices are computerised in the UK (Lawrenson *et al*., 1999). There are many computer software systems available which have the facility to generate prescriptions and maintain records of diagnoses, symptoms, consultations, referral letters, test results and demographic data. All data which can be abstracted from general practice databases are anonymised to ensure patient confidentiality.

4.1.1.Description of GP databases in UK

In the UK, computerised databases derived from general practice medical records have been extensively used for research. The most widely used are the General Practice Research Database (GPRD), the Health Improvement Network (THIN), IMS Disease Analyzer (IMS DA), QRESEARCH, and Doctor's Independent Network (DIN). Another database the Tayside Medicines Monitoring Unit (MEMO) has also been used for epidemiological research, but this database is relatively small and contains anonymised patient data only from one region in Scotland. The Fourth Survey of Morbidity in General Practice (MSGP4) is another relatively small general practice database which contains data on approximately 502,000 patients from 60 practices in England and Wales. The MSGP4 provides individual level demographic, socioeconomic, ethnicity, and a complete record of consultations with GPs, however there is no prescribing information in this database (McCormick *et al*., 1995).

There are other routinely collected data that could be used for research and other purposes such as the Yellow Card Scheme (collects spontaneous reports of adverse drug reactions), Prescribing Analysis and Cost (PACT) data, and NHS Prescription Services (formally known as Prescription Pricing Authority) (http://www.nhsbsa.nhs.uk/). Hospital episode statistics (HES) is another data source which has been frequently used by researchers; HES only provides hospital admission data in England. Analyses and summarised tables are published annually on their website (http:www.doh.gov.uk/hes/). The data structure of HES is based on admission episodes not patient-level. It needs to be noted that one patient may have more than one episode of illness in HES data, therefore it is not possible to identify whether individual patients have a single or multiple hospital episodes. Despite being valuable sources of data for research, data sources such as the Yellow Card Scheme and PACT are not useful for epidemiological research such as disease prevalence or drug prescribing patterns.

It is beyond the scope of this thesis to cover all these computerised databases in detail, the next section is restricted to an overview of longitudinal patient-level databases from general practice in the UK: General Practice Research Database (GPRD), the Health Improvement Network (THIN), IMS Disease Analyzer (IMS DA), QRSEARCH, Doctors' Independent Network (DIN), and Tayside Medicines Monitoring Unit (MEMO). A summary of these databases is presented in Table 4.1., which describes individual databases in more detail as well as their strengths and limitations. A brief description of each of these databases is given below.

Table 4.1: Clinical database from primary care in the UK

Database	Year Started	Population covered	No. of Practice	Area covered	Website
General Practice Research Database (GPRD) (also known as FF-GPRD)	1987	Approx. 9 million patients (5.2 million active patients)	630	England, Scotland, Wales and Northern Ireland	www.gprd.com
The Health Improvement Network (THIN)	2003	Approx. 9 million patients (3.4 million active patients)	479	England, Scotland, Wales, and Northern Ireland	www.epic-uk.org
QRESEARCH	1990	Over 13 million patients	660	England, Scotland, Wales, and Northern Ireland	www.qresearch.org
IMS Disease Analyzer (IMS DA) (formerly MediPlus)	1992	3 million patients	125	England, Scotland, Wales, and Northern Ireland	www.imshealth.com
Doctors' Independent Network (DIN)	1989	Over 3 million patients	Over 300	England and Wales	NA
Tayside Medicines Monitoring Unit (MEMO)	NA	Over 400,000 patients	320	Tayside region of Scotland	http://www.dundee.ac.uk /memo/

Abbreviation: FF-GPRD, Full Feature General Practice Research Database; NA, not available.

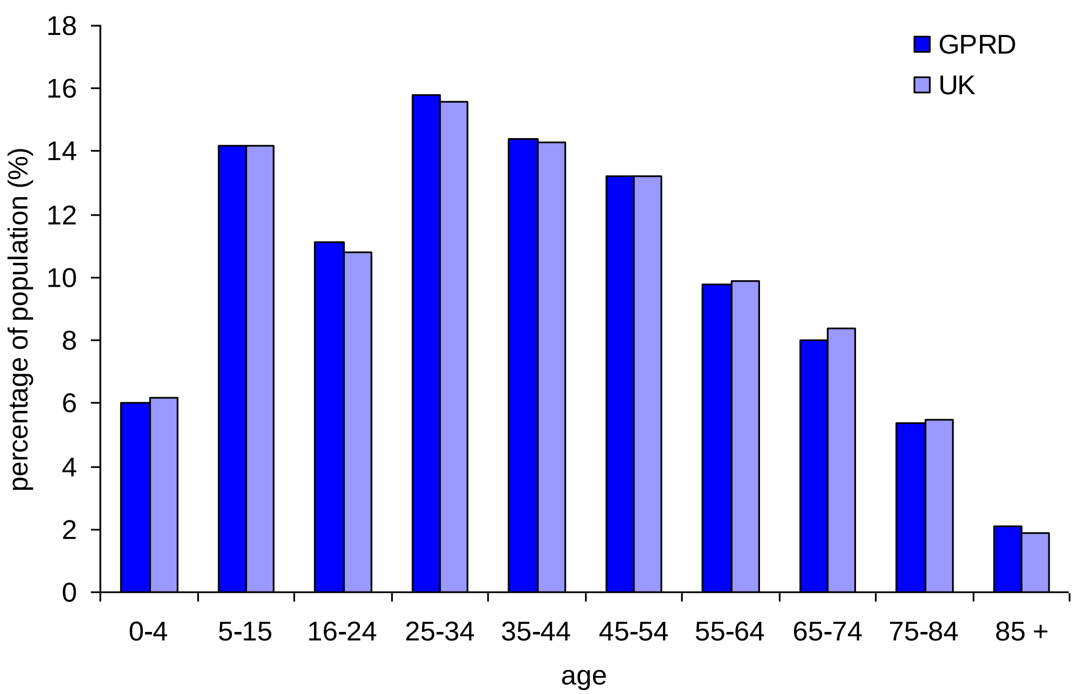
4.1.2.The General Practice Research Database (GPRD)

The General Practice Research Database (GPRD) was initially developed by Dr Alan Dean in 1987. Data were provided from contributing practices and the amount and quality of the data have increased over the years. Most data are considered to have reached research standard ('up-to-standard'). Data for the GPRD are collected from GPs using the practice management software, the Value Added Medical Products (VAMP) software, which was designed by the VAMP Ltd software company. GPs enter data using VAMP software which enables them to contribute anonymised data to a central database. Therefore, it was previously known as the VAMP General Practice Research Database (VAMP-GPRD) (Lis & Mann, 1995). There are currently two versions of the GPRD operating in parallel: the original VAMP software GPRD, and newly developed Full Feature GPRD (FF-GPRD). However, the VAMP-GPRD is gradually being phased out since the FF-GPRD currently provides external linkage with other national databases (e.g. disease registry, Hospital Episode Statistics). The GPRD group is updating the FF-GPRD data from the VAMP GPRD in order to include complete historical data in the current database.

The participating GPs submit records at regular intervals, following the agreed guidelines for recording clinical and prescribing data. In 1993, Reuters Health Information acquired VAMP Ltd, and subsequently donated the database to the Department of Health (DoH) for health research purposes on a non-profit making basis and the database were renamed the GPRD. Since then, the database has been managed by the UK DoH. At present it is maintained by the Medicines and Healthcare products Regulatory Agency (MHRA). All research proposals that request data from the GPRD need to be approved by the GPRD's Scientific and Ethical Advisory Group (SEAG) which was set up in 1995. This has subsequently been replaced by the Independent Scientific Advisory Committee for MHRA database research (ISAC), which was set up in 2006. The purpose of this committee is to review protocols of GPRD research and ensure that the study methodologies are well-defined and patient confidentiality is protected. In March 2012, the GPRD was renamed the Clinical Practice Research Datalink (http://www.cprd.com/intro.asp) but at the time of writing this thesis it was known as the GPRD which is used throughout the thesis.

The GPRD is a large consolidated database of general practice clinical records in the UK. The GPRD contains anonymised computerised information entered by GPs in their clinical practices. This database comprises anonymised patient and practice-level data; thus individual patients are not named and cannot be identified from the computer system. All patients in the database are given a unique anonymised identifier, which can only be decoded by the practice. The computerised information includes demographics, diagnoses from specialist referrals, prescriptions, hospital admissions, consultations, and the results of laboratory tests. The database contains information on over 4.5 million active patients, equivalent to approximately 7.4% of the UK population. The age and sex distribution of the patient population in the database at any point in time is broadly representative of the population in England and Wales (Figure 4.1).

Figure 4.1: A comparison of the GPRD population with the England and Wales population in 1998 (data source: Office for National Statistics 1998)



The demographic distribution of the GPRD is broadly representative of that of the UK; thus analysis of GPRD prescribing data will provide information on GP prescribing trends that are generally representative of national GP prescribing trends. The database is also able to provide a denominator to estimate prevalence and incidence. Studies on mortality, hospital admissions, cancer registration and prescribing have yielded similarities to the population in terms of age and sex distribution from other sources such as Office for National Statistics (ONS), and the Prescription Pricing Authority (PPA) (Hansell *et al*., 1999; Hollowell, 1997).

The following information is available from the GPRD:

- Demographic records: year of birth, gender, date of registration
- Clinical records: these contain medical diagnoses which are coded using the Oxford Medical Information System codes (OXMIS) and Read codes.
- Therapy records: these contain all prescriptions issued by GPs. Prescribed drugs are coded using Multilex®[2]. Information on drug name, prescribing date, duration, dose, route of administration, number of pacts dispensed, and daily quantity are all recorded.
- Referral records: these contain information on secondary or tertiary referrals.
- Test records: these include results from laboratories.
- Immunisation records: all vaccines are listed.
- Miscellaneous information, including smoking status, height, weight, BMI, and other lifestyle factors such as alcohol consumption, may also be listed.

Two systems, both hierarchical, are used for coding clinical symptoms and diagnoses known as OXMIS disease classification and Read clinical terms (Perry, 1978; Chisholm, 1990). Read is a comprehensive clinical coding system and was specifically devised for GPs to use in UK practice. It also has procedural and administrative terms therefore it allows more accuracy in recording than OXMIS. In 1995, Read was introduced to the Vision software (a practice management software) and OXMIS were gradually phased out. Table 4.2 shows the main branch of Read code classification (Dave & Petersen, 2009).

[2] Multilex® is a dictionary which classifies products using unique codes and is maintained by First DataBank.

Table 4.2: The main branch of Read code classification

1	History & symptoms
2	Examination and signs
3	Diagnostic procedures
4	Laboratory procedures
5	Radiology & physics in medicine
6	Preventative procedures
7	Operations, procedures & sites
8	Other therapeutic procedures
9	Administration
A	Infectious and parasitic diseases
B	Neoplasms
C	Endocrine, nutrition, metabolic and immunity disorders
D	Disease of blood and blood forming organs
E	Mental disorders
F	Nervous system and sense organ diseases
G	Circulatory system diseases
H	Respiratory system diseases
J	Digestive system diseases
K	Genitourinary system diseases
L	Complications of pregnancy, childbirth and the puerperium
M	Skin & subcutaneous tissue disease
N	Musculoskeletal and connective tissue diseases
P	Congenital anomalies
Q	Perinatal conditions
R	Symptoms, signs and ill-defined conditions
S	Injury & poisoning
T	Causes of injury and poisoning
U	External causes of morbidity and mortality
Z	Unspecified conditions

As for data quality control, the internal check is continually assessed by an automated audit before being uploaded into a central database. A quality measure referred to as the "Up To Standard (UTS)" is applied. This warrants that the data meets quality standards at patient and practice level. The criteria for assessment are listed below (MHRA, 2010):

- An empty or invalid first registration date.
- Absence of a record for a year of birth.
- A first registration date prior to their birth year.
- A transferred out reason with no transferred out date.
- A transferred out date with no transferred out reason.
- A transferred out date prior to their first registration date.
- A transferred out date prior to their current registration date.
- A current registration date prior to their birth year.
- A gender other than female/male/indeterminate.
- An age of greater than 115 at end of follow up.
- Recorded health care episodes in years prior to birth year
- Registration status of temporary patients.

If any of the above applies, the patient is considered 'unacceptable' and is not recommended for inclusion in a research dataset. Validation studies have shown that the quality and completeness of the data is high (Hollowell, 1997; Walley &Mantgani, 1997).

The GPRD also provides a verification service for researchers to obtain more information on patients. Researchers can request copies of hospital letters, discharge summaries, death certificates and post-mortem reports through GPRD. Questionnaires can also be sent to GPs to obtain detailed information regarding patients' conditions. In order to protect patient confidentiality, all data returned to researchers from the GPRD are anonymised. GPRD is a population-based database of primary care in the UK. It provides a rich source of longitudinal data from general practices, and it has the advantage of data collected at the time of the event, including demographic information, clinical event and prescriptions. Data from over 4.4 million patients are held on the database; the findings from the GPRD can be generalised to represent UK practices. In addition, this large computerised database can be used broadly and efficiently to investigate rare conditions. As the GPRD contains data only from primary care practices, there are certain limitations. There is no coded information on hospital admissions such as reason for admission, length of stay, or drug use during inpatient episodes. In addition, there are no over-the-counter (OTC) prescriptions recorded in the database. The GPRD does not have a direct link of prescriptions to clinical diagnoses, which is a recognised limitation in many computerised databases (Wong & Murray, 2005). Although the GPRD has limitations, the database is of high quality with a large sample size, and has therefore been extensively used for research worldwide.

4.1.3. IMS Disease Analyzer (IMS DA)

The IMS (previously known as Intercontinental Medical Statistics), is an international healthcare information company, collecting anonymised health information within the UK and across the world. The database IMS Disease Analyzer (formally known as Mediplus) is one of the largest longitudinal clinical databases in the world and was first established in 1992. The purpose of setting up this database was for research (De Lusignan *et al*., 2002). In the UK, IMS DA contains approximately 2 million anonymous patient records and over 95 million prescriptions from about 125 general practices with more than 500 general practitioners (Strom *et al*., 2006). Patient data in IMS DA are anonymised at practice-level and consist of patient demographics, indications for treatment and prescription details. Prescribed drugs are coded based on the Anatomical Therapeutic Chemical (ATC) classification issued by the European Pharmaceutical Market Research Association (EpMRA), and medical diagnoses are coded to Read code (a UK medical diagnostic code) which can be linked to the International Classification of Disease (ICD) version 10 Codes (WHO, 2010).

The following information is also collected in the UK IMS DA:

- ***Practice data:***

1. Regional Health Authority
2. Town Size
3. Patients per practice in the current quarter
4. Patients per practice in the last quarter
5. Drug-dispensing flag
6. Number of doctors

- ***Doctor data:***

1. Active status
2. Age
3. Sex
4. Date of birth
5. Doctor registration year
6. Trainer status

- ***Patient data:***

1. Age, sex, height, weight and BMI
2. Marital status
3. Registration status
4. Regional Health Authority

- ***Consultation day: date of visit***
- ***Clinical records: medical diagnoses are coded using Read code and ICD 10 codes:***

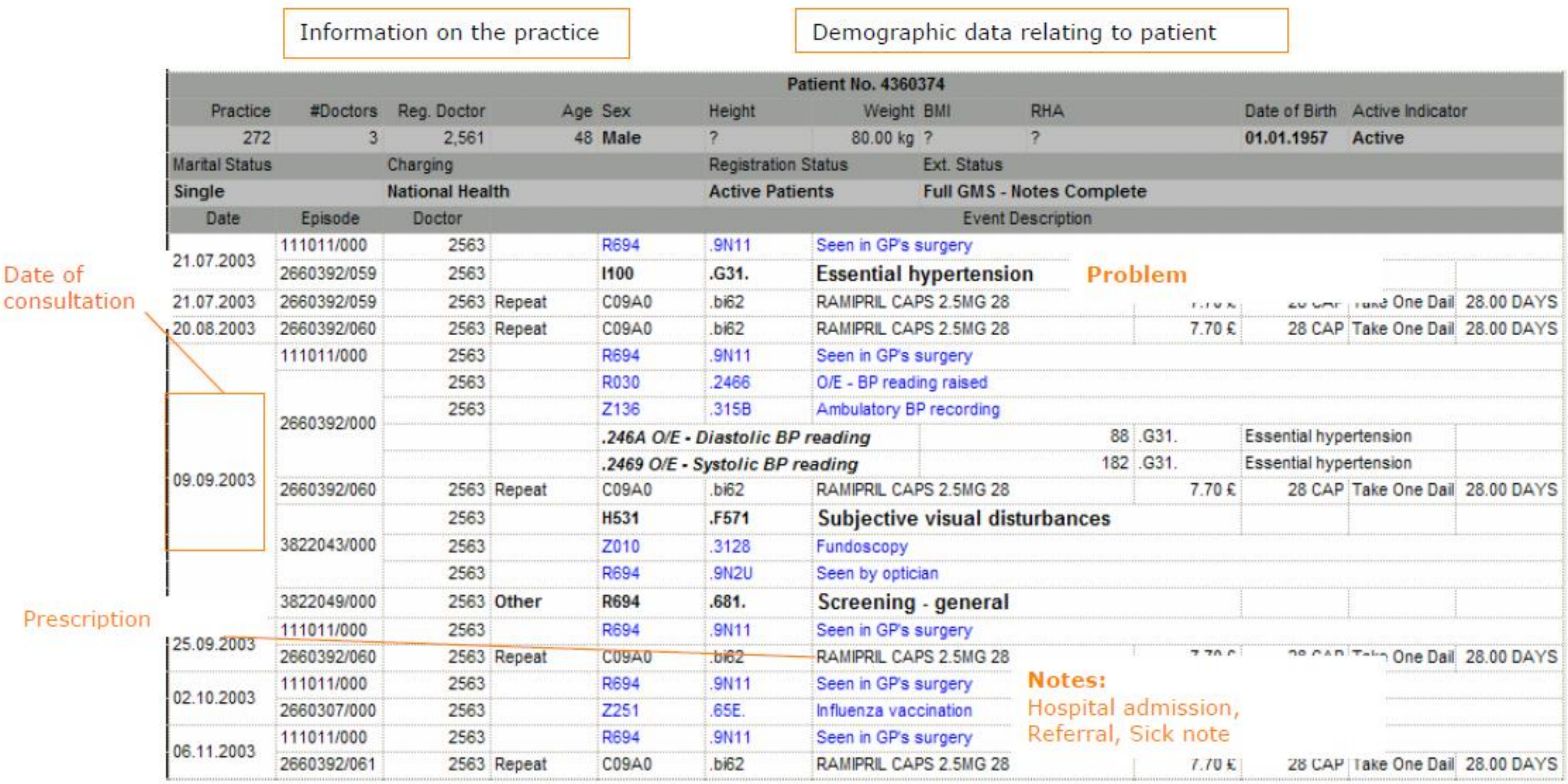
1. Read codes and text (level 1 to 5)
2. ICD-10 codes and text (level 1 to 4)
3. Referral records
4. Sick notes
5. Tests
6. Further diagnosis and symptoms
7. History of or family history

- ***Therapy records:***

1. Medication
2. Manufacturer
3. ATC (levels 1 to 4)
4. Product (brand and generic name)
5. Pack form
6. Therapy text (Read code)
7. Price
8. Pack size, form and strength
9. Recommended dosages
10. Therapy stop

Figure 4.2 shows a typical medical record for a patient in the IMS DA database. The IMS DA has a direct link between prescriptions and the medical diagnosis which is different from other primary care databases. However, there is no information on hospital outcomes and OTC prescriptions in IMS DA. This database has a similar potential to the GPRD in drug utilisation studies and risk assessment studies (e.g. case-control studies) (Clayton *et al*., 2008). The IMS DA is subject to internal validation and quality checks and is consistent with other UK prescription counts (Langman *et al*., 2001). In order to improve data recording quality, data quality markers are used to ensure that only data that reaches specific quality standards are included in IMS DA. The data quality markers are based on ten different assessment criteria, as outlined in Table 4.3. GPs will receive payment as incentive for their time in providing quality data for IMS DA. As the quality of data recorded in IMS DA is high, it has been widely used in paediatric medication research in Europe in recent years (Sturkenboom *et al*., 2008; Hsia *et al*., 2009; Neubert *et al*., 2010; Neubert *et al*., 2011; Sen *et al*., 2011; Hsia *et al*., 2012).

Figure 4.2: Example of medical record for a patient in UK IMS DA (reproduced with permission from UK IMS)



Patient No. 4360374										
Practice	#Doctors	Reg. Doctor	Age	Sex	Height	Weight	BMI	RHA	Date of Birth	Active Indicator
272	3	2,561	48	Male	?	80.00 kg	?	?	01.01.1957	Active

Marital Status	Charging	Registration Status	Ext. Status
Single	National Health	Active Patients	Full GMS - Notes Complete

Date	Episode	Doctor				Event Description						
21.07.2003	111011/000	2563		R694	.9N11	Seen in GP's surgery						
	2660392/059	2563		I100	.G31.	Essential hypertension						
21.07.2003	2660392/059	2563	Repeat	C09A0	.bi62	RAMIPRIL CAPS 2.5MG 28					One Dail	28.00 DAYS
20.08.2003	2660392/060	2563	Repeat	C09A0	.bi62	RAMIPRIL CAPS 2.5MG 28			7.70 £	28 CAP	Take One Dail	28.00 DAYS
09.09.2003	111011/000	2563		R694	.9N11	Seen in GP's surgery						
	2660392/000	2563		R030	.2466	O/E - BP reading raised						
		2563		Z136	.315B	Ambulatory BP recording						
				.246A O/E - Diastolic BP reading			88	.G31.	Essential hypertension			
				.2469 O/E - Systolic BP reading			182	.G31.	Essential hypertension			
	2660392/060	2563	Repeat	C09A0	.bi62	RAMIPRIL CAPS 2.5MG 28			7.70 £	28 CAP	Take One Dail	28.00 DAYS
	3822043/000	2563		H531	.F571	Subjective visual disturbances						
		2563		Z010	.3128	Fundoscopy						
		2563		R694	.9N2U	Seen by optician						
	3822049/000	2563	Other	R694	.681.	Screening - general						
25.09.2003	111011/000	2563		R694	.9N11	Seen in GP's surgery						
	2660392/060	2563	Repeat	C09A0	.bi62	RAMIPRIL CAPS 2.5MG 28					One Dail	28.00 DAYS
02.10.2003	111011/000	2563		R694	.9N11	Seen in GP's surgery						
	2660307/000	2563		Z251	.65E.	Influenza vaccination						
06.11.2003	111011/000	2563		R694	.9N11	Seen in GP's surgery						
	2660392/061	2563	Repeat	C09A0	.bi62	RAMIPRIL CAPS 2.5MG 28			7.70 £	28 CAP	Take One Dail	28.00 DAYS

Table 4.3: The ten data quality markers used by IMS DA database (modified from De Lusignan et al., 2002)

Quality Marker	Reasons for its inclusion
1. Percentage of registered patients for whom there has been a change in the record over the previous 12 months	An indication that the system is being used routinely
2. Percentage of patients with year of birth and sex recorded	Ensures that researchers can analyse disease by age and sex of patient
3. Percentage of problems or diagnoses with Read Code of level 3 or lower	Lower-order codes represent more specific diagnoses. Some high-order contain negatives within the lower orders
4. Percentage of notes linked to problem or diagnosis	Linkage of notes increasingly important for analysis of test results
5. Percentage of notes in which Read Code is level 3 or lower	As marker 3
6. Number of prescriptions issued per week per 1000 registered patients	This is a crude measure of how much prescribing is not being recorded in database. Also looking for abnormalities in trends over time that would allow detection of missing data
7. Complete dose and regimen details related to dose-effect or adverse drug reactions (ADR)	Important for prescribing analyses
8. Proportion of acute prescriptions issued linked to a problem title or diagnosis	A key function of the database is to show what the prescribing
9. Proportion of repeat prescriptions linked to a problem title or diagnosis	A key function of the database is to show the prescribing behaviour of general practitioners
10. Ratio of acute prescriptions issued to chronic prescriptions	Checks for consistent usage

4.1.4.EPIC The Health Information Network (THIN)

EPIC (Epidemiology Pharmacology Information Core) is a commercial research company established in 1994, specialising in the collection of patient data from general practice within and outside UK. The Health Improvement Network (THIN) has been collecting patient records in the UK continuously since 2003. The latest dataset contains information on over 7.7 million patients from 546 general practices (October 2011) in the UK which use the Vision software system to record their consultations. This amounts to over 41 million patient years of computerised data. As both GPRD and THIN use the same computer management software (Vision), there is approximately 50% overlap of the general practices between the two databases (personal communication); therefore the THIN database structure is similar to the GPRD. Patient data in THIN are anonymised at practice-level and include demographics, details from general practitioner's visits, diagnoses from specialist referrals and hospital admissions, prescriptions and the results of laboratory tests. The Read classification is used to code specific diagnoses, and a drug dictionary based on data from the MULTILEX classification is used to code drugs.

The THIN database also contains anonymised comments and other information such as Townsend deprivation scores (used for social deprivation). Currently, EPIC is working with a specialist data privacy company to develop a methodology which will enable THIN to link with secondary care such as Hospital Episode Statistics (HES), cancer data, cause of death data and dispensed prescription information.

THIN contains clinical primary care data, covering approximately 5.7% of the UK population. Similar to GPRD, the demographic distribution of THIN is broadly representative of that of the UK. All data are held anonymously, with patient identifiers removed. Similar to GPRD, EPIC also offers a facility on follow up questionnaire research. This service is subject to a fee paid by researchers via EPIC to GPs. Researchers can also obtain further clarification and validation of patient medical records such as copies of death certificates, discharge details, hospital letters, and free text information through EPIC. All data sent to the researchers from the EPIC verification service is anonymised to protect patient confidentiality.

The data collected in THIN are audited regularly and participating general practices are subjected to a number of quality checks. One unique indicator in this database is "acceptable mortality reporting (AMR)". The AMR is used to indicate the year from which a practice's mortality records are deemed complete, this indicator can be used to avoid biases related to "immortal period" (Maguire *et al*., 2008). This immortal period is defined as no observed deaths in the practice although deaths were expected during this period. An example is that in a practice, no deaths were observed prior to data conversion to the new computer software. Apparently the practice only kept the medical records of patients who were alive at the time data conversion took place. Currently, over a hundred papers have been published in peer-reviewed journals using the THIN database.

4.1.5.QRESEARCH

QRESEARCH is another medical record database composed of anonymous data collected from general practitioners. It is owned by the University of Nottingham and EMIS (Egton Medical Information Systems; a supplier of software management for primary care). It contains data from 660 practices and includes information on over 13 million patients in the UK, equivalent to approximately 21% of the UK population. Historical data are recorded in the database from as early as the 1990s. The QRESEARCH database also has a well-defined population with longitudinal data and is representative of the UK population in age, gender and geography (www.qresearch.org). This database has been set up on a not-for-profit basis with no intention of being in a commercial relationship with pharmaceutical companies and other industry. The QRESEARCH database is currently the largest computerised database of anonymised patient data from general practices in the UK.

4.1.6.The Doctors' Independent Network (DIN)

The Doctor's Independent Network (DIN), an anonymised computerised database in the UK was established in 1989. Of the national computerised primary care databases, DIN is less well known. The DIN database collects practice records from over 300 general practices in the UK, equating to over 3 million patients using Torex (formerly known as MEDITEL) software (Carey *et al*., 2004). Data available from DIN include patient demographics, prescription details and indications for treatment. Prescribed drugs and diagnoses are coded using Read codes. DIN also contains a socio-economic indicator based on individual patient postcodes, which differs from that used by the GPRD where a patient's socio-economic status is recorded only at the practice-level, not the individual patient level. A validation study showed that age and sex structure of DIN is similar to that of England and Wales (Carey *et al*., 2004), but most of the practices contributing to the DIN database are from southern England. Although DIN provides a unique source of population-based clinical information, it is used mainly by pharmaceutical companies to investigate trends of drug prescribing (Carey *et al*., 2004).

4.1.7.The Medicines Monitoring Unit (MEMO)

The Medicines Monitoring Unit (MEMO) is a university-based organisation that uses record-linkage techniques to undertake pharmacoepidemiologic and pharmacovigilance research in Tayside, Scotland (Evans *et al*., 1995; Evans *et al*., 1999). The population of Tayside is approximately 400,000 people (Evans *et al*., 1995). The patient population contained within MEMO is demographically similar to that of the rest of Scotland (Evans *et al*., 1999). This database contains data generated within the National Health Service in Scotland (NHSiS) and all prescriptions dispensed in Tayside. Morbidity data include inpatient hospital admissions, biochemical tests, cancer registration, death certificates, and diagnostic procedures (MacDonald *et al*., 1995). This database provides useful data although it only covers one region in Scotland and is smaller than its other computerised counterparts. However, the data in MEMO may not be representative of the UK population as a whole.

4.1.8.Summary of primary care databases

Table 4.4 summarises the detailed information recorded in these databases as well as their strengths and limitations. In general, the computerised GP databases have the advantages of longitudinal records and detailed prescribing data. In recent years, those databases have been broadly and intensively used for epidemiological research. As these databases provide historical data, it can also shorten the time to conduct a study compared to a prospective study design, which may require up to several years to recruit enough patients to obtain robust estimates. Also, the large size of the databases permits the study of rare diseases. Despite the strengths of computerised GP databases, there are general limitations that need to be addressed. Most databases contain referral and hospital admission information. However, it is unclear which specialist confirmed the diagnoses and/or symptoms at the time of onset of the condition. It has been estimated that 95% of prescriptions issued by GPs are recorded in both GPRD and IMS DA databases (formally known as MediPlus) (Lawrenson *et al*., 1999). As medical records and prescriptions are entered by GPs in primary care, medications prescribed by specialists in hospitals (e.g. secondary care, tertiary care), or by GPs at home visits and controlled drugs such as methadone, may be incomplete (Lawrenson *et al*., 1999). In addition, there is no information on treatment compliance as with all observational data and over-the-counter (OTC) prescriptions are not recorded in the databases. A general limitation of primary care databases is that prescriptions and indications data are not directly linked, except in the IMS DA database.

Table 4.4: Summary table of primary care databases in UK:

Database	Computer system used	Data collected	Strengths	Limitations
General Practice Research Database (GPRD) (also known as FF-GPRD and Clinical Practice Research Datalink)	VAMP system	-Demographic information* -Symptoms and diagnoses -Prescriptions issued -Referral records -Laboratory tests and results -Immunisation records -Miscellaneous information: smoking, height, weight, BMI, alcohol consumption	1. Data are broadly representative of national population (covers about 7.4% of UK population). 2. The quality and completeness of recording are high and validity have been reported to be high (Walley & Mantgani, 1997; Nazareth *et al*., 1993a,b; Jick *et al*., 1991). 3. Additional services are provided by the GPRD group such as questionnaires to GPs to obtain further information. 4. Data have been widely used by researchers and over 890 articles published in peer-review journals.	1. Data are primarily collected for clinical management not for research purposes. 2. It requires intensive training to use data and also knowledge of relational databases. 3. License for accessing data is expensive. 4. There is no information on hospital data, length of stay and prescriptions. 5. Over-the-counter (OTC) prescriptions are not recorded. 6. Prescription records are not directly linked with diagnoses. 7. Information on individual socioeconomic status and ethnicity are not recorded.
The Health Improvement Network (THIN)	In practice systems (INPS)	-Demographic information -Symptoms and diagnoses -Prescriptions issued -Referral records -Laboratory tests and results -Immunisation records -Miscellaneous information: smoking, height, weight, BMI, alcohol consumption -Socioeconomic data: postcode, Townsend score quintile	1. Data are broadly representative of national population (covers 5.7% of UK population). 2. The database contains useful 'Acceptable Mortality Reporting' filter to avoid the danger of "immortal period" bias (Maguire et al., 2009) 3. Anonymised comments and Townsend deprivation scores are available. 4. Additional service are offered such as questionnaires to GPs to obtain further information.	1. Data are primarily collected for clinical management not for research purpose. 2. There is no information on hospital tests, length of stay and prescriptions. 3. Cost of using the data is high. 4. Over-the counter (OTC) prescriptions are not recorded. 5. Ethnicity is not recorded. 6. No direct link between prescriptions and diagnoses. 7. The database was newly available so little validation work had been conducted at the time.

Continued.

QRESEARCH	EMIS clinical computer system	-Demographic information -Symptoms and diagnoses -Prescriptions issued - smoking, height, weight, BMI	It is operated on a not-for-profit basis and the main interest is "supporting non-commercial research which will improve patient care" (www.qdscore.org)	1. There is no information on hospital tests, length of stay and prescriptions. 2. Over-the-counter (OTC) prescriptions are not recorded. 3. There is no information on ethnicity
UK IMS Disease Analyzer (IMS DA)	Meditel system	-Demographic information -Symptoms and diagnoses -Prescriptions issued -Referral records -Immunisation records -Laboratory tests and results	1. Data are broadly representative of the UK population (covers 3% of UK population). 2. There is a direct link between prescriptions and diagnoses. 3. The validity and completeness of data reported to be high (Lawrenson et al., 1998) 4. Symptoms and diagnoses are cross-mapped to ICD codes.	1. Information on socioeconomic status and ethnicity are not recorded. 2. There is no information on hospital tests, length of stay and prescriptions. 3. Over-the-counter (OTC) prescriptions are not recorded.
Doctors' Independent Network (DIN)	iSOFT software (formerly Torex)	-Demographic information -Diagnostic information -Prescriptions issued -Referral records -Immunisation records -Socioeconomic indicator (the ACORN index)	1. Data are broadly representative of England and Wales' population. 2. Socioeconomic measure is based on individual level not practice level.	1. There is no information on hospital tests, length of stay and prescriptions. 2. Over-the-counter (OCT) prescriptions are not recorded. 3. It only contains data from England and Wales. 4. Most of the practices in DIN are in the South of England.
Tayside Medicines Monitoring Unit (MEMO)	NA	-Demographic information -Diagnostic information -Prescriptions issued (from both GP practice and hospitals)	1. It contains prescriptions issued during hospital admissions and prescriptions dispensed in Tayside primary care. 2. It contains cancer registration and death certificate information.	1. It contains data from only one Scottish region, so it may not be representative of the UK population as a whole.

*Demographic information: age, gender, registration date, de-registration date. NA: not available.

4.1.9.Utility of GP databases in research

Data from large computerised clinical databases such as claims databases and automated medical record databases have been extensively used for epidemiological studies in the USA and Canada since the late 1970s (Strand *et al*., 1994; Hershel, 1997). An example on the process of using computers to automate information is presented in Figure 4.3.

Figure 4.3: An example of the process of generating computerised data for research (adopted from De Lusignan & Weel, 2006)

Implement computerised medical records with: 1. A reliable denominator 2. The capability to be searched	→	The system provides: 1. Data about the quality of care and clinical practice 2. Information about the epidemiology of the condition	=	Using informatics for: 1. Clinical audit 2. Health service planning 3. Research

In order to derive data from a computer system to answer a specific question, researchers should be able to use data extraction tools which extract data based on their research questions. Furthermore, researchers should have strong programming skills to manipulate large datasets in an appropriate statistical package in order to model longitudinal data (Lawrenson *et al*., 1999). Once data have been extracted, data cleaning should be performed which should include cross checking to identify unexpected patterns, recording errors or duplication. The acquisition of data extraction is shown in Fig 4.4.

Figure 4.4: The general technical process of data extraction from a computerised database (adopted from De Lusignan & Weel, 2006)

Define system architecture: 1. Unique patient identifiers 2. Problem orientated records 3. Linkage: conditions to treatment 4. Coding system 5. Develop any prompting or decision support	→	1. Develop technical means of data extraction 2. Ensure information security/data protection 3. Extracted data can be mapped to existing data about condition in question	→	Defined processes for data: 1. Aggregation ensuring referential integrity 2. Cleaning processing 3. Analyses

A crucial concern for the user of computerised database is validity, which includes completeness and accuracy of recording. This key attribute for recorded diagnoses and prescriptions in general practice databases needs to be addressed before carrying out a study. One example is to verify that patients with a certain recorded diagnosis in the database actually have that condition. Further confirmation to verify that patients have that diagnosis can be obtained by going back to their GPs or by requesting a hospital summary. This approach is time-consuming and it can also be expensive. Several validation studies have been carried out using GPRD and IMS DA for various conditions. Furthermore, to improve the quality of data contained in GPRD and IMS DA, GPs receive reimbursement for their time (Lawrenson *et al*., 1999; De Lusignan *et al*., 2002). GPs receive approximately £400 per year as an incentive to meet the data quality score for ten assessment criteria in IMS DA (De Lusignan *et al*., 2002).

In April 2004, a new General Medical Service (GMS) contract was introduced into general practice: the Quality and Outcomes Framework (QOF). This new pay-for-performance scheme was expected to have profound implications to improve the quality of care in primary care. It was a voluntary incentive scheme for GP practices. To measure achievement, GPs have to enter and maintain high quality information from their clinical practice system. The scheme started in 2004 and included 136 quality indicators (DoH, 2004b). The QOF has four domains, also known as indicators, to measure the achievement: clinical, organisational, patient experience, and additional services. The overall achievement of a practice would be measured through a points system, and payment would be based on points achieved. In order to qualify for payment, information entered has to be recordable, reliable, consistent and auditable (Roland, 2004). Therefore, data recording by GPs was expected to improve. However, there is currently insufficient evidence to demonstrate whether the QOF improves patient care and data recording in GP practices.

Despite the concerns about data validity, computerised databases have been extensively used in North America for pharmacoepidemiological research since the 1970s. These have routinely collected data and have also been used in research such as incidence and/or prevalence of disease in community (disease epidemiology), pharmacoeconomics, and health service research (Strom *et al.*, 2006). This information will enable researchers, clinicians, and policy makers to identify the gap between practice and evidence. In the past, the lack of resources available for pharmacoepidemiologic research in the UK was highlighted (Hall, 1992). A study by Black *et al*. (2004) showed that most electronic databases were not being utilised for research and it concluded that more support was needed in the UK, because routinely collected data from general practice should be used beyond clinical management. In recent years, there has been a surge in the use of computerised databases for pharmacoepidemiologic studies in the UK (Wong & Macey 2005).

Pharmacoepidemiology is a relatively new field and it is defined as: 'the study of the use and the effects of drugs in a large population' (Strom *et al*., 2006). It applies epidemiological methods in the area of clinical use of drugs in populations. Pharmacoepidemiologic studies can be broadly divided into drug utilisation studies, post-marketing surveillance, hypothesis-testing studies (e.g. case-control study) (Hall, 1992; Hennessy, 2006; Smeeth *et al*., 2006). The advantage of using computerised databases is that they enable medical research to be carried out in a large sample of a particular population that would normally be excluded from clinical trials, such as children and pregnant women. For instance, a report by the Medical Research Council, the UK Department of Health and the Association of the British Pharmaceutical Industry recommended that clinical databases should be used for paediatric medication research (Royal College of Paediatrics & Child Health, 2004).

Drug utilisation studies are increasingly being used in pharmacoepidemiology. A drug utilisation study is defined by the WHO as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (WHO, 2000). This study design can be used to monitor the patterns of drug prescribing during the post-marketing phase as it is impossible to predict this at the pre-marketing clinical trial phase. Drug utilisation studies can be divided into two types: quantitative or qualitative. Quantitative drug utilisation studies are used to quantify the present state, developmental trends, and time course of drug usage in a large population. Qualitative drug utilisation studies are used to assess the appropriateness of drug use by linking prescription data to the reasons for prescribing (e.g. diagnosis) (Lee *et al*., 2006). The pharmacoepidemiologic studies described in this thesis are mainly drug utilisation studies.

4.1.10.Summary

Prior to the development of computerised databases, it was a complex and expensive process to identify and follow-up a large cohort of patients to measure disease prevalence and examine prescribing trends. Currently, computerised databases from general practice allow researchers to conduct studies with a large sample size and more complete medical and prescription data, as well as historical records. In addition, it is considered to be a more cost-effective and less time consuming approach compared to traditional field study. Although the primary intention for developing GP databases was to manage patient care in the clinical setting, it is also an invaluable source of data for research.

The clinical computerised databases from general practice used for the studies described in this thesis have provided us with large cohorts of patients receiving anti-obesity drugs and have enabled us to investigate trends in drug utilisation in the UK. Although there are several GP databases in the UK and all have their own advantages and limitations for conducting pharmacoepidemiological research, the work conducted in this thesis primarily utilised data retrieved from the GPRD and IMS DA. Various methods of data manipulation and statistical analysis were used to analyse the data for these drug prescribing studies conducted in primary care; they are described in detail in each of the sections.

4.2.Drug utilisation of orlistat, sibutramine and rimonabant in general practice

4.2.1.Introduction

As discussed previously, there were three drugs approved for obesity treatment in adults in the UK between 1999 and 2006: orlistat (licensed in 1999), sibutramine (licensed in 2001) and rimonabant (licensed in 2006). The NICE guidelines (2006) recommended that orlistat and sibutramine should be considered as useful adjuncts to lifestyle modification in adolescents ≥12 years old with physical co-morbidities, but use in <12 years old should be reserved for those with life-threatening co-morbidities. The NICE guidelines do not recommend rimonabant for obese young people. This may be due to limited data on rimonabant use in young people at the time NICE guideline was released, as rimonabant was licensed for obesity treatment in adults in 2006. Prior to 2007, there was no information on anti-obesity drug prescribing patterns (orlistat, sibutramine, rimonabant) in children and adolescents in the UK. Although rimonabant and sibutramine were withdrawn from the EU market after the start of this project in 2008 and 2010, respectively, the experience of their prescribing patterns and use could be useful for future anti-obesity drug prescribing in this population. Therefore, data on the prescribing patterns of these drugs were also included in our study. A drug utilisation study was conducted to investigate the prescribing patterns of orlistat, sibutramine, and rimonabant, in chidlren and adolescents, in primary care in the UK between 1999 and 2006.

4.2.2.Aim and objectives

The aim of this study was to investigate the prescribing patterns of orlistat, sibutramine and rimonabant in young people in primary care. This was achieved by investigating annual, sex- and age-specific prevalence of anti-obesity drug prescribing in children and adolescents aged 0-18 years between January 1999 and December 2006.

4.2.3.Methods

4.2.3.1.Data Source

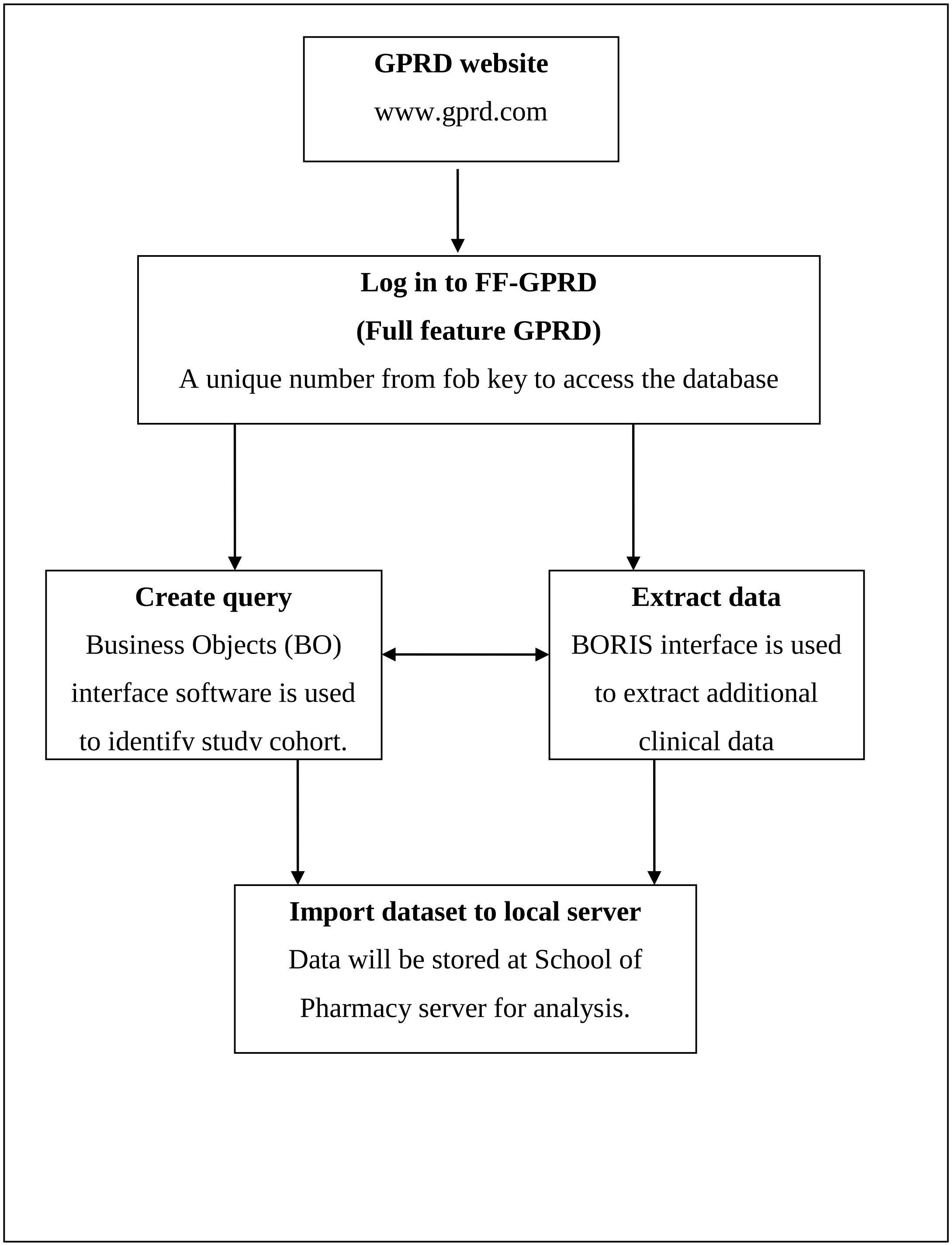
As described in section 4.1.2, the GPRD is a longitudinal primary care database maintained by the MHRA. At the time of our study in 2007, the database contained anonymised patient records for approximately 5% of the UK population. Detailed information on the database structure is described in section 4.1.2. The study population comprised all children and adolescents with at least 6 months' data, who received at least one prescription for an anti-obesity drug in the study period, between January and December 2006.

4.2.3.2.Data extraction

The GPRD is a relational database, it is necessary to link all datasets to produce a complete patient dataset for data analyses (Appendix 4). An online GPRD (FF-GPRD) enables researchers to access the full range of raw data in the GPRD. An online medical browser extraction tool, Business Objects and Business Objects Information Systems (BORIS), is provided by the GPRD which acts as an interface between researchers and the database. This medical browser allows researchers to create queries for specific questions in their research area. Figure 4.5 illustrates an overview of how data are obtained and processed from the central database to create a master dataset for analysis. All the databases were imported onto the local server at the School of Pharmacy, where data cleaning and merging of these databases were carried out. In order to create appropriate queries to retrieve information, criteria were defined based on the aim and objectives of this project. In this study, a number of steps were undertaken to extract data on the use of anti-obesity drugs in the UK.

The study cohort was comprised of patients who had received orlistat, sibutramine, or rimonabant. The first step of data extraction was to compile a comprehensive list of study drug codes. Once the list of drug codes was collated, the second step was to enter these codes into Business Objects (BO) query to retrieve information on patients who had received these drugs during the study period. Appendix 5 illustrates the details of the BO query to retrieve all patients under 19 years old who had ever been issued anti-obesity drug prescriptions during the study period. The third step was to carry out data cleaning. Once the data had been retrieved from the GPRD, the process of data cleaning was performed which involved crosschecking duplicates and unexpected recording patterns in the database. The statistical software (Stata/MP version 10) was used to clean the dataset.

Figure 4.5: Flowchart of data extraction from the GPRD

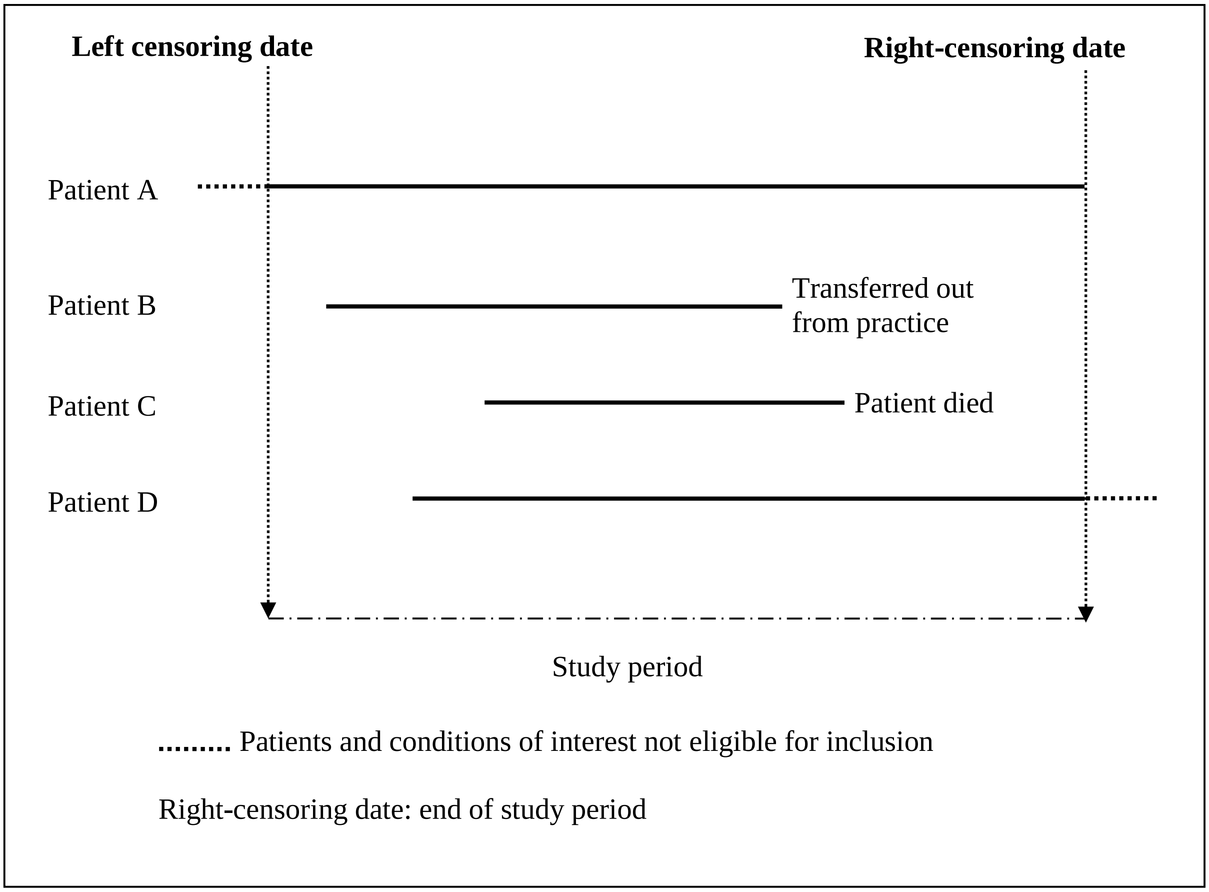


4.2.3.3.Calculation of Prevalence

In an epidemiology study, prevalence is defined as the proportion of patients in a population who have the disease at a specific time (Hennekens & Buring, 1987). To use this concept in a pharmacoepidemiological study the number of patients who were receiving a certain drug(s) during a particular time period is calculated. In these analyses, annual prevalence was defined as the number of patients with at least one anti-obesity drug prescription during the year of investigation divided by the total number of patient-years (aged 0-18 years) in the same year. Patient-years are defined as the sum of the number of years contributed by each patient at risk of being prescribed an anti-obesity drug during the study period in the study population (children and adolescents aged 0-18 years). The sex- and age-specific prevalence was calculated as the number of patients receiving at least one anti-obesity prescription during the year of investigation divided by the total number of patient-years in the same year stratified by age and gender.

In order to calculate patient-years, the censoring date for each individual patient needs to be determined. Patients may enter or leave the study at various points in time and are only eligible for inclusion in the study between their respective ‘left-censoring’ and ‘right-censoring’ dates in the database. This means that not all patients will be included in the study throughout the whole study period. The left-censoring and right-censoring dates can be used to calculate the length of time that each patient was contributing data to the database. Figure 4.6 illustrates the process of data censoring in the GPRD primary care database. The date of left-censoring date is referred to as: 1) study start date, or 2) patient date of registration, or 3) practice up-to-standard date (e.g. GPRD). The right-censoring date is defined as the date data cease to be contributed to the database, this may be when patients left or transferred out of the practice or died.

Figure 4.6: Schematic of censoring dates in database

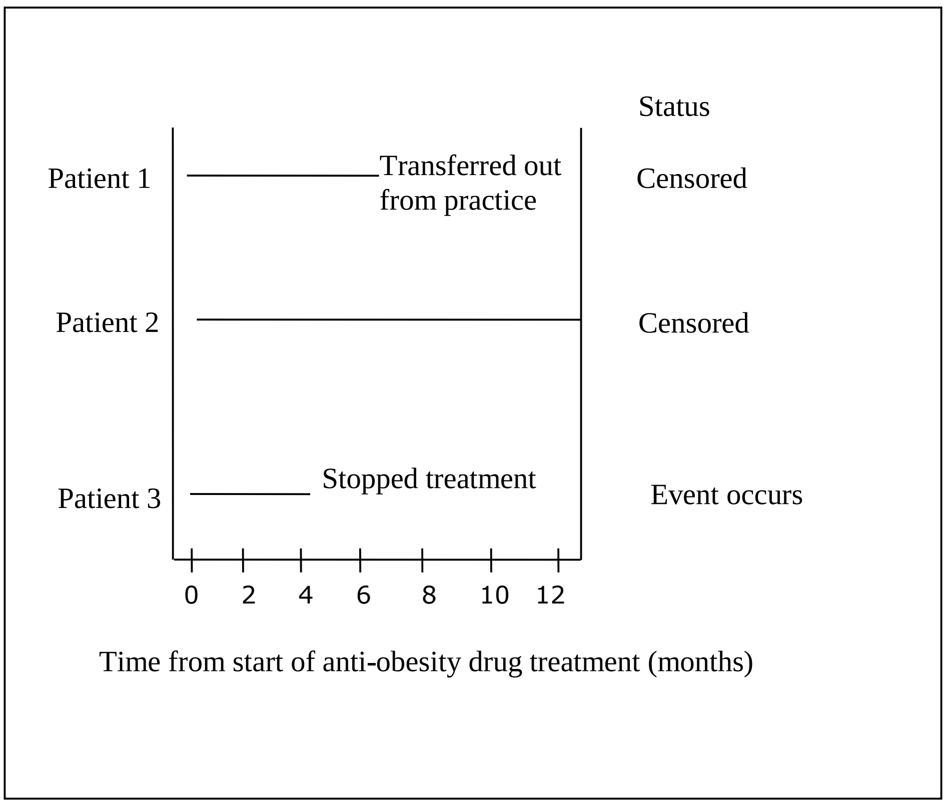


A Chi-squared test (Cochran–Armitage test for trend) was used to examine if changes in prevalence of prescribing were significant. Ninety-five percentage Confidence Intervals (95% CI) were generated using Poisson approximation. P-values of <0.05 were considered statistically significant.

4.2.3.4.Treatment duration of anti-obesity drugs

The duration of anti-obesity drug treatment was analysed using the Kaplan–Meier survival method and Log-rank test. Kaplan-Meier survival analysis is widely used for cancer studies to measure the time to an event of interest (i.e. death), and the term for the time to event of interest is *survival time* (Altman, 1990). This statistical analysis can also be applied to other medical studies to analyse 'time-to-event' data, meaning that the data have an end point time when the event occurs (Jager *et al*., 2008). Figure 4.7 illustrates survival times for patients from the study cohort who received anti-obesity drugs.

Figure 4.7: Schematic of duration of anti-obesity drug treatment



The distinctive feature of survival analysis is that the event of interest will probably not occur at the end of study period. In the above illustration (Figure 4.7), Patient 1 will be censored as this person referred out from practice during the study period. The survival time of Patient 2 would also need to be censored at the end of study period as we don't know when this person will stop anti-obesity drug treatment. The censoring can also happen for other reasons such as lost to follow-up during the study period. Survival time of Patient 3 will not be censored as this patient stopped treatment (event of interest) during the study period.

In this study, treatment was considered to have stopped if there were no further anti-obesity prescriptions issued within 90 consecutive days (3 months) after the date of the last anti-obesity prescription. Study subjects were censored either if the end of the study period was within 90 consecutive days after their last anti-obesity prescription or if they had left the practice without stopping treatment.

The logrank test was performed in this study to compare treatment duration between anti-obesity drugs. The Logrank test is used to compare survival time between groups. This test can detect whether the event of interest is consistently greater in one group than another (Altman, 1990; Jager *et al*., 2008). It should be noted that the Logrank test is mainly one of significance and it cannot estimate the difference in size between the groups (Altman, 1990).

4.2.3.5.Obesity related co-morbidities

Information on obesity related co-morbidities was also examined in the dataset for study subjects prescribed one of the anti-obesity drugs. Given the range of conditions potentially associated with obesity, the search for obesity related co-morbidities was restricted to hypertension, dyslipidaemia, insulin resistance syndrome (metabolic syndrome) and depression. Data were manipulated and analysed using Stata version 11.0 (College Station, TX, USA).

4.2.3.6.Ethical Approval

The GPRD study protocol presents in Appendix 6 and approval for this study was granted by the GPRD's Scientific and Ethnical Advisory Group (Appendix 7).

4.2.4.Results

A total of 452 children and adolescents received 1,334 prescriptions for anti-obesity drugs between January 1999 and December 2006. As there was only one prescription for rimonabant (in a patient aged 18 years in 2006), further analyses refer only to orlistat and sibutramine. Orlistat made up 78.4% (n=1,045; 1,045/1,334) of all prescriptions. The majority of prescriptions were issued to female patients (82.3%; 372/452). The mean age at which patients were first prescribed an anti-obesity drug was 17.0 years (SD 1.33; range 10-18 years). For female patients, the mean age at first prescription was 17.1 years (SD 1.27); for male patients, the mean age was 16.7 years (SD 1.53). The median number of anti-obesity drug prescriptions per subject was 2.0 (inter-quartile range 3.0), and 40.5% (n=183) of patients received only one anti-obesity prescription during the study period.

The number of patients who received an anti-obesity drug steadily increased between 1999 and 2006, particularly for female patients (Table 4.5). Figure 4.8 shows the number of prescriptions by calendar year. The use of both orlistat and sibutramine increased rapidly after each drug was introduced into the UK clinical practice. The number of orlistat prescriptions rose from 10 to 282 per year between 1999 and 2006, a 28-fold increase. From 2001 to 2006, the number of sibutramine prescriptions rose from 8 to 128, a 16-fold increase.

Table 4.5: Description of study subjects between 1999 and 2006 by gender and calendar year

	Number of patients			Person-years for total study population*		
Year	Boys	Girls	Total	Boys	Girls	Total
1999	1	4	5	421,126.3	403,384.2	824,510.4
2000	5	12	17	477,904.7	458,427.2	936,331.9
2001	12	32	44	532,525.5	510,634.9	1,043,160.3
2002	14	44	58	569,844.4	546,502.5	1,116,346.9
2003	8	43	51	595,658.5	571,827.6	1,167,486.2
2004	11	53	64	634,025.4	609,673.3	1,243,698.7
2005	12	80	92	666,092.6	643,415.1	1,309,507.8
2006	18	103	121	681,887.7	660,069.4	1,341,957.1

*Person-years: the sum of the number of years contributed by the total population in the database aged 0-18 years, during each year of the study period (1999-2006).

Figure 4.8: Number of anti-obesity prescriptions to children and adolescents aged 0-18

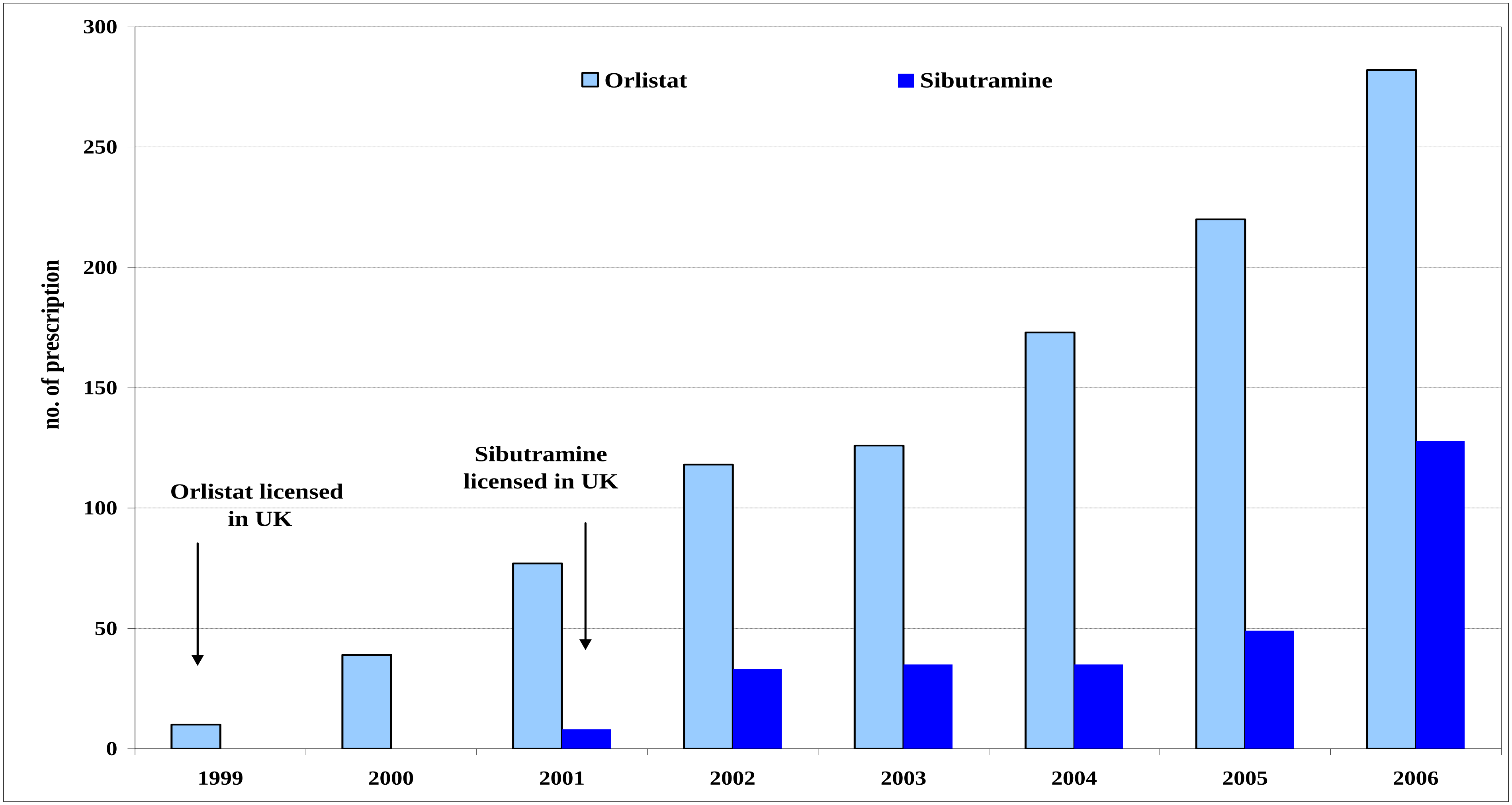


Figure 4.9 shows the prevalence of overall anti-obesity prescribing by calendar year and gender for children and adolescents aged 0-18. Overall use of anti-obesity drugs significantly increased from 0.006 per 1000 person-years (95%CI 0.0007 to 0.0113) in 1999 to 0.091 (95%CI 0.07 to 0.11) in 2006 ($p < 0.0001$), a 15-fold increase. Similar increases were seen in both genders over the study period, increasing in girls from 0.009 (95%CI 0.0001 to 0.019) to 0.156 (95%CI 0.126 to 0.186) ($p<0.0001$), and in boys from 0.002 (95%CI 0.0019 to 0.004) to 0.027 (95%CI 0.012 to 0.04) ($p<0.02$).

Figure 4.10 shows the age-specific prevalence of anti-obesity prescribing by gender. No anti-obesity drugs were prescribed to children aged <10 years, although 25 prescriptions were issued to children aged < 11 years old. Prescribing rose with increasing age, particularly from 14 years onwards in both boys and girls.

Figure 4.9: Sex-specific annual prevalence of anti-obesity drug prescribing in children and adolescents aged 0-18

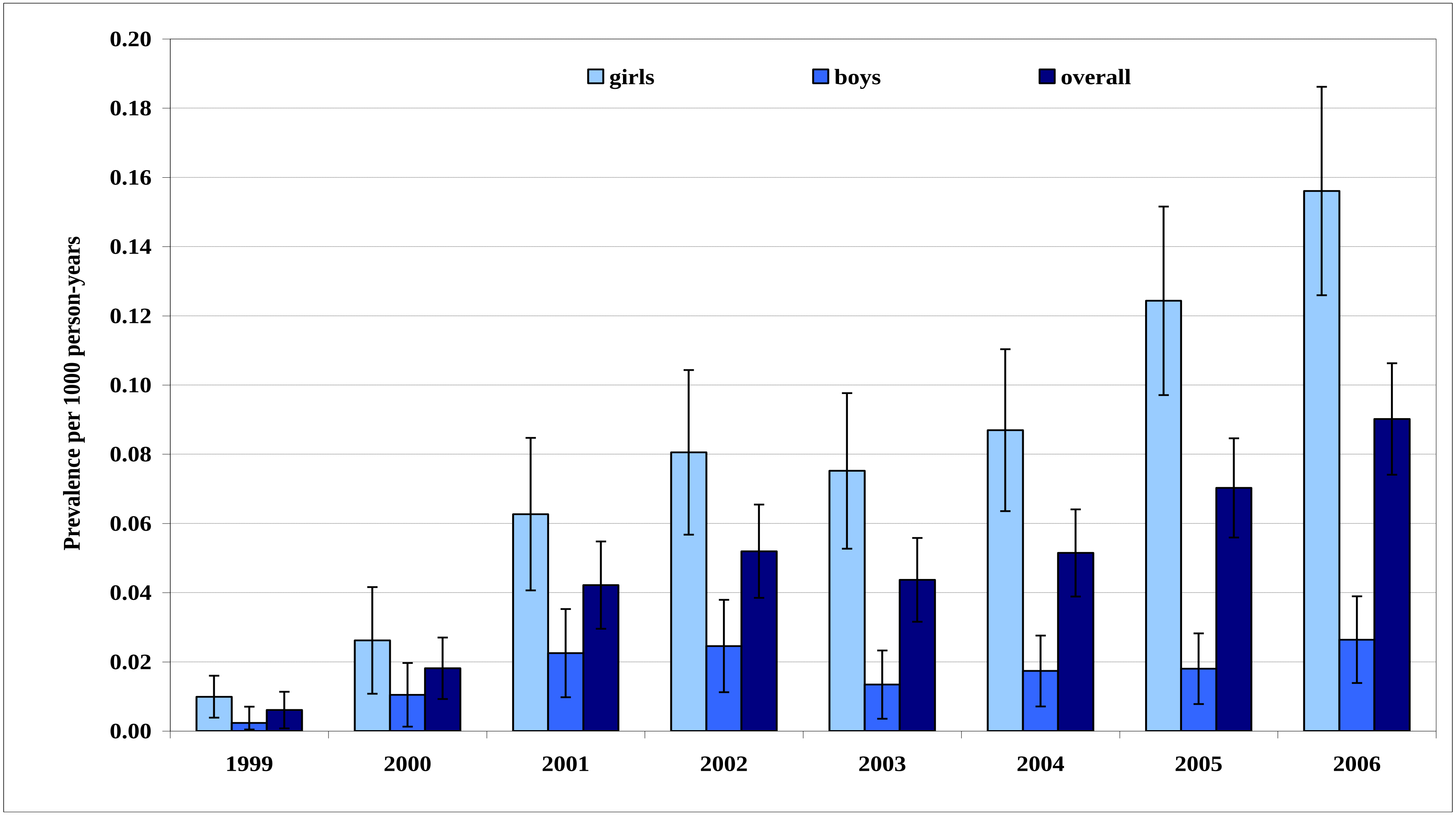


Figure 4.10: Age-specific prevalence of anti-obesity drug prescribing in children and adolescents

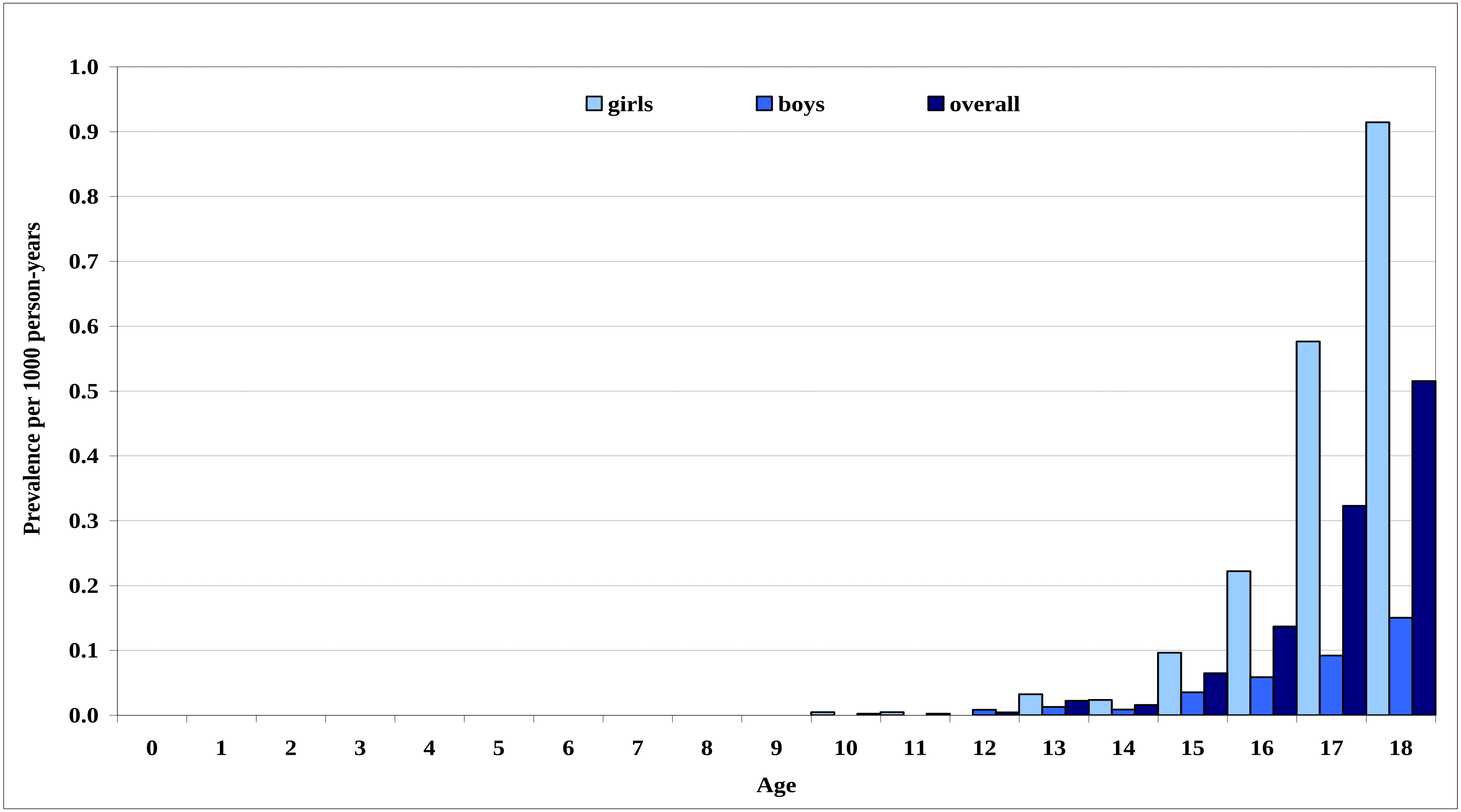
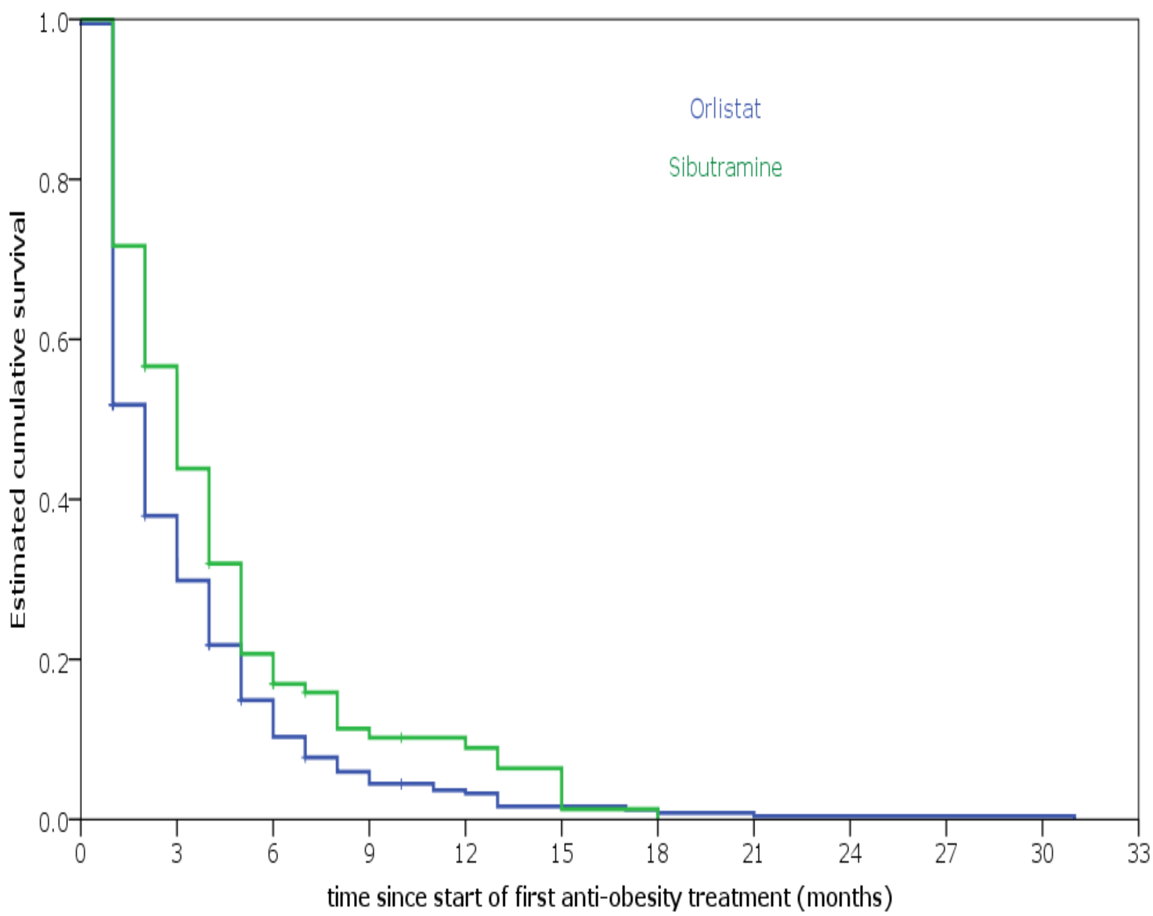


Figure 4.11 shows Kaplan-Meier survival curves for treatment duration for orlistat and sibutramine. The mean duration of orlistat use was significantly shorter (3.0 months; 95%CI 2.72-3.47) compared with sibutramine (4.2 months; 95%CI 3.4-5.0) ($p<0.003$). Approximately 45% of patients who received orlistat were discontinued within the first month, with about 10% remaining on treatment after 6 months. Approximately 25% of patients who received sibutramine were discontinued within the first month, with less than 20% remaining on drug use at 6 months.

Figure 4.11: Kaplan-Meier survival curves for children and adolescents who received anti-obesity drug treatment



Thirty-nine patients were prescribed both orlistat and sibutramine; 34 patients were initially prescribed orlistat and subsequently switched to sibutramine, and five patients initially received sibutramine and then switched to orlistat. Reasons for changing between anti-obesity drugs were not available in the database.

Table 4.6 shows specific obesity-related co-morbidities in those prescribed anti-obesity drugs. We identified 22 patients with diabetes in the study population. Those patients all received anti-diabetic drug treatment (either insulin or oral hypoglycaemic drugs).

Table 4.6: Selected obesity-related comorbidities within the population treated with anti-obesity drugs

Co-morbidity diagnosis	**% (n)**
Diabetes mellitus	4.9 (22)
Hypertension	2.2 (10)
Depression	28.5 (129)
Polycystic ovarian syndrome*	7.5 (28/372 female study subjects)

*Polycystic ovarian syndrome: only for girls in study population.

4.2.5.Discussion

This study has demonstrated that prescribing of anti-obesity drugs in children and adolescents has increased dramatically between 1999 and 2006. The results showed that in 2006 approximately 0.1 per 1000 of those aged ≤18 years were being prescribed anti-obesity drugs. Generalising across the UK population of 13,928,000 persons aged ≤18 years, this would suggest that approximately 1300 young people were prescribed anti-obesity drugs annually. However, persistence with these drugs past the first month was strikingly poor, and only 25% of those prescribed orlistat and 35% of those prescribed sibutramine remained on the drug for longer than 3 months, generally regarded as an adequate time to ascertain whether significant weight loss has occurred.

Orlistat and sibutramine were not licensed for obesity treatment in children and adolescents in the UK. A rapid increase in prescribing for children and adolescents of off-label anti-obesity drugs was demonstrated, which in most cases are discontinued before patients can reasonably expect to see a clinical benefit. Furthermore, this pattern of drug use is likely to be significantly wasteful of resources, as anti-obesity medications are relatively expensive (Shrishanmnganathan *et al*., 2007). Although orlistat and sibutramine have shown significant but limited benefits for weight reduction and have reported good tolerability in a small number of randomised placebo-controlled trials in young people, evidence for their effectiveness in large populations of young people is largely lacking (Molnar, 2005). The 2006 NICE guidance on the use of sibutramine and orlistat was based on very limited effectiveness data. Further research into effective and safe use of anti-obesity drugs in children and adolescents outside of efficacy trials is needed. Investigation of the reasons for discontinuation of anti-obesity drugs may allow the development of support strategies that minimise the occurrence of adverse drug reactions and maximise drug continuation when used in young people.

4.2.6.Strengths and limitations

The GPRD contains robust data on prescriptions issued in primary care, and given the universal nature of the NHS in the UK, our estimates of population prescribing prevalence in primary care are highly likely to be sound and generalizable to UK primary care. However, several limitations need to be highlighted. Firstly, the GPRD records prescriptions issued in primary care only, excluding drugs issued from hospitals. However, the vast majority of anti-obesity drugs are prescribed from primary care in the UK in both adults and children (Shrishanmuganathan *et al*., 2007), although often under the advice of hospital specialists. In children and young people, the NICE guidance (2006) suggests that anti-obesity drugs should be initiated by specialist paediatric services but that continuation of prescribing is appropriate in primary care. It is thus possible that our data do not include a very small number of initial hospital prescriptions; unfortunately, there are no data to investigate the extent of hospital prescribing. Secondly, the GPRD does not contain data on socioeconomic status and ethnicity, thus precluding analysis of their impact on prescribing patterns. Thirdly, we had no access to data regarding reasons for discontinuation of anti-obesity drug treatment. However, given that the commonest causes of drug discontinuation are lack of efficacy and adverse effects, we believe that it is reasonable to speculate that discontinuation occurred due to either of these factors. A further limitation is the lack of data on BMI. Whereas weight was recorded frequently in the database, there were relatively few recordings of height for most patients. As a result, we were unable to calculate accurate BMI data in relation to prescription dates and thus could not assess either the mean BMI of patients received anti-obesity drugs, or the change in BMI in those who received treatment.

4.2.7. Comparison with the literature

This is the first known published study using population-based data on prescriptions to investigate the trends and patterns use of orlistat and sibutramine in children and adolescents in the UK. The only comparable data on prescription prevalence is from a report of total national prescription counts in England from 1998 to 2005, which were not broken down by age but are almost certain to be mainly for adults for whom the use of anti-obesity drugs is licensed. This study found a 25-fold increase in orlistat prescriptions and a 4-fold increase in sibutramine prescriptions between 1998 and 2001 (Shrishanmuganathan *et al*., 2007). A similar increase in orlistat prescriptions in children and adolescents was also identified (28-fold increase from 1999) with a much larger increase (16-fold increase from 2001) in sibutramine prescriptions. The orlistat prescriptions outnumbered those for sibutramine by approximately four to one over our study period; however, this was likely to be an artefact of the earlier introduction of orlistat. In 2006, there were approximately twice as many prescriptions for orlistat as sibutramine, similar to the ratio described for adults (Shrishanmuganathan *et al*., 2007).

The only comparable data on tolerability and persistence with orlistat and sibutramine in children and young people comes from a small number of efficacy studies. For orlistat, published reports conclude repeatedly that it is 'well tolerated' (McDuffie *et al*., 2002; Chanoine *et al*., 2005; Henness & Perry 2006) in children and adults. However, published trial data show that although persistence with orlistat for ≥3 months in clinical trials was markedly greater than in our data, gastrointestinal side-effects were reported in >50% (Chanoine *et al*., 2005). The largest study of orlistat in adolescents, a randomized placebo-controlled study of 539 subjects over 12 months, reported that 65% (232/357) of those randomised to orlistat completed 12 months' treatment, and that only 2% (2/357) in the orlistat arm dropped out due to adverse reactions. However, gastrointestinal adverse events were reported by 50% of those taking orlistat (Chanoine *et al*., 2005). A detailed study of the tolerability of taking orlistat together with a comprehensive behavioural and dietetic programme in 20 adolescents over 3 months found that 85% completed 3 months on orlistat, but that 50–60% reported a combination of unpleasant gastrointestinal side-effects (McDuffie et al., 2002). In a small open-label randomized controlled trial, gastrointestinal side-effects were reported in all 22 adolescents receiving orlistat, of whom seven (32%) dropped out of the trial during the first month due to side-effects attributable to orlistat (Ozkan *et al*., 2004).

Similarly, for sibutramine, published studies report that this drug is generally well tolerated in adolescents (Berkowitz *et al*., 2003; Berkowitz *et al*., 2006; Godoy-Matos *et al*., 2005). The largest trial, a randomised placebo-controlled trial in 498 obese adolescents over 12 months, reported that 76% of those in the sibutramine arm continued the drug for the full 12-month trial period, with only 6% of subjects withdrawing because of adverse events (Berkowitz *et al*., 2006). In a smaller randomised controlled trial of 60 obese adolescents over 6 months, 93% completed the 6-month trial and no subjects withdrew due to sibutramine side-effects (Godoy-Matos *et al*., 2005). In a further small randomised trial of 46 obese adolescents, 81% (21/26) in the sibutramine arm completed the 6-month trial, and none withdrew because of adverse events (Garcia-Morales *et al*., 2006).

Findings in our analysis do not support the above reports on tolerability of and persistence with orlistat and sibutramine. In contrast, our results showed that in general clinical use, only one-third of patients continued treatment past 3 months. Although we do not have data on reasons for discontinuation, this is likely to reflect either poor therapeutic efficacy of the drug in the young people, and/or lower level of parental education, and high frequency of side-effects due to excessive intake of dietary fat (Molnar, 2005) or, alternatively, unrealistic expectations of rapid major weight loss, leading to discontinuation when this is not achieved. Although we have no data on reasons for discontinuation in our study, evidence suggests that both orlistat and sibutramine are less well tolerated and more rapidly discontinued in children and adolescents than in highly selected, motivated and supported clinical trial populations. These differences may reflect the routine weight management support programmes that were an integral part of many of the clinical trials of orlistat and sibutramine (McDuffie *et al*., 2002; Chanoine *et al*., 2005; Berkowitz *et al*., 2006; Godoy-Matos *et al*., 2005).

A further reason for early discontinuation in patients in our study may have been the relatively high proportion (approximately 29%) with a comorbid diagnosis of depression, as feelings of hopelessness and negativity may contribute to early discontinuation of the drug. Although we have no further information about the validity of recorded diagnoses of depression, this figure is higher than the 13% reported from population-based estimates of psychological distress in obese UK adolescents (Viner *et al*., 2006). This suggests that in clinical practice, obese adolescents with significant psychological distress may be over-represented in those prescribed anti-obesity drugs. Children <12 years old were found to be prescribed anti-obesity drugs, contravening the Summary of Product Characteristics (SPC), and very few patients in our analysis continued their anti-obesity drug for a 6- to 12-month trial suggested by NICE. We also found that the number of girls received anti-obesity drugs was higher than boys in our study. This sex ratio is similar to that seen in a population-based study of anti-obesity drug use in Taiwanese adults (Liou *et al*., 2007), and reflects well-described higher proportions of body-weight concerns in adolescent girls (Taylor *et al*., 2005).

4.2.8.Conclusion

This study shows that prescriptions of off-label anti-obesity drugs in children and adolescents have dramatically increased between 1999 and 2006. However, the majority of these drugs were rapidly discontinued before patients could see a clinical benefit, suggesting they are poorly tolerated or less efficacious when used in young people, in contrast to findings from clinical trials. The early discontinuation of treatment in this study is unclear. Further research into the long-term efficacy and safety of anti-obesity drugs in children and adolescents is needed. In addition, a further study should investigate the reasons for early discontinuation of these drugs in this population.

4.2.9.Issues leading to investigation of metformin prescribing in children and adolescents

As discussed previously (Chapter 1), due to the withdrawal of rimonabant in 2008 and sibutramine in 2010, there are several drugs that have been considered for potential obesity treatment. Of these drugs, metformin has been recommended as the best choice of drug for the treatment of obesity as these patients are more likely to have metabolic syndromes (e.g. diabetes) (Viner *et al.,* 2005). Therefore, the popularity of metformin for obesity therapy in clinical practice may have increased. In addition, there is no evidence on its use in children and adolescents from general practices in the UK. Therefore, the prescribing trend for metformin and the indications for its use in the primary care setting were examined and are reported in the next section.

4.3. Metformin prescribing patterns to young people in primary care in the UK

4.3.1. Introduction

Metformin is the most commonly prescribed oral anti-diabetic drug for diabetes mellitus (DM) in children and adolescents in the UK (Hsia *et al*., 2009). As metformin has been shown to be effective in reducing testosterone levels and improving irregular menstrual cycles (Harwood *et al*., 2007), it has also been prescribed for the treatment of polycystic ovarian syndrome (PCOS) in women of reproductive age (Ehrmann, 2005; Mastorakos *et al*., 2006). In two large randomised controlled trials (RCTs) metformin was shown not to be more efficacious than placebo in adult women with PCOS (Moll *et al*., 2006; Legro *et al*., 2007), whereas its effectiveness in treating PCOS in adolescent girls has been shown in several RCTs (Ibáñez *et al*, 2004; Bridger *et al*., 2006; De Leo *et al*., 2006). However, in contrast to these findings, a recent RCT did not show benefit from metformin treatment along with lifestyle modification in adolescents with PCOS (Hoeger *et al*., 2008). For both women and adolescent girls there is still controversy regarding metformin use in the treatment of PCOS. However, despite the controversy, metformin is still recommended as one of the therapeutic options for PCOS in teenage girls (Harwood *et al*., 2007).

In addition to its use in treating PCOS, studies have shown that metformin is associated with moderate BMI reduction in obese non-diabetic adolescents (Rogovik *et al*., 2010; Park *et al*., 2009). In the UK, metformin is licensed only for children aged over 10 years with type 2 diabetes who have failed strict dieting (BNFC, 2011). At present, metformin is not licensed for the treatment of PCOS or obesity in adults or children in the UK (BNFC, 2011; BNF, 2011; SPC). Little is known about the extent to which this drug has been used in young people in UK primary care. Therefore, this study was conducted to examine metformin prescribing patterns in children and adolescents in the UK primary care setting.

4.3.2.Methods

A retrospective cohort study was conducted using the IMS Disease Analyzer (IMS DA) database which was described earlier in this thesis (Chapter 4.3.1). This cohort study consisted of children and adolescents aged <19 years registered with a GP who contributed data to the IMS DA between January 2000 and December 2010. All subjects needed to have a minimum of six months' valid data in the database; this is to ensure that patients were not temporarily registered with a practice in the database. Age bands were based on a modification of the International Conference of Harmonization (ICH) classification as follows: < 2, 2-11, 12-15 and 16-18 years (Rose & Stotter, 2007).

Annual prevalence of metformin prescribing was calculated as the total number of subjects with at least one prescription of metformin during each year of investigation divided by the total number of person-years in the same year, using Poisson distribution with a 95% confidence interval and stratified by age and gender. A Chi-square test (Cochran-Armitage test for trend) was used to examine the yearly trend of metformin prescribing. As IMS DA directly links prescriptions to medical indications, the following were examined for metformin prescriptions: diabetes (ICD10 E10-E14), PCOS (E282), and obesity (E66). Analyses were carried out using Stata/MP version 11.0 (College Station, TX, USA).

4.3.3.Ethical Approval

The IMS study protocol presents in Appendix 8 and approval for this study was granted by the IMS Independent Scientific and Ethical Advisory Committee (see Appendix 9).

4.3.4.Results

A total of 2,674 metformin prescriptions were issued to 337 children and adolescents for all indications, between January 2000 and December 2010. The majority of patients who received metformin were female (80%; 270/337). There were no metformin prescriptions issued to children aged less than 2 years. More female adolescents aged 12-18 years received metformin than other age groups (Table 4.7). The overall annual prevalence of metformin prescribing increased from 0.03 per 1000 person-years (95% CI 0.02 to 0.05) in 2000 to 0.16 per 1000 person-years (95% CI 0.12 to 0.20) (p=0.001) in 2010 (Figure 4.12).

There were 290 patients with at least one diagnosis of DM, PCOS and/or obesity in their medical records, of which 235 patients were female (81%) (Table 4.8). Of these 290 patients, 120 female patients were prescribed metformin for the treatment of PCOS and obesity. Also there were 23 female patients with diagnoses of DM, PCOS and obesity who received metformin treatment during the study period. There were 22 patients (7.6%; 22/290) who were prescribed metformin for obesity treatment alone. A total of 47 patients were prescribed metformin without either a specific diagnosis or relevant diagnosis; after scrutinising their medical records, the most common diagnosis for prescribing was “unknown and unspecified causes of morbidity”. As the IMS DA only contains data from GPs, there are no hospital records in the database to verify diagnoses for these prescriptions.

Table 4.7: Age and gender of patients in cohort by calendar year, 2000 to 2010

	Aged <2		Aged 2-11		Aged 12-15		Aged 16-18			Person-years for total study population*		
Year	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Total	Boys	Girls	Total
2000	0	0	2	4	0	3	1	10	20	266,537.2	257,100.8	523,638.0
2001	0	0	1	9	1	3	5	18	38	265,419.0	256,182.8	521,601.7
2002	0	0	4	5	2	7	1	18	37	263,778.0	254,243.0	518,020.9
2003	0	0	7	5	7	10	3	29	61	258,312.5	248,746.9	507,059.4
2004	0	0	5	7	6	15	2	38	73	244,468.2	235,088.5	479,556.7
2005	0	0	5	6	5	9	5	34	64	233,251.9	223,886.7	457,138.6
2006	0	0	7	8	5	9	5	41	75	226,924.2	218,008.5	444,932.7
2007	0	0	1	6	4	11	3	41	66	219,137.0	210,379.6	429,516.6
2008	0	0	4	6	1	15	10	29	65	211,939.1	203,246.9	415,186.0
2009	0	0	2	4	3	14	7	28	58	201,208.5	192,740.3	393,948.8
2010	0	0	3	3	3	13	5	34	61	191,773.4	183,644.6	375,418.0

*Person-years: the sum of the number of years contributed by the total population in the database aged 0-18 years, during each year of the study period (1999-2006).

Figure 4.12: Annual prevalence of metformin prescribing in children and adolescents aged 0-18 years by calendar year

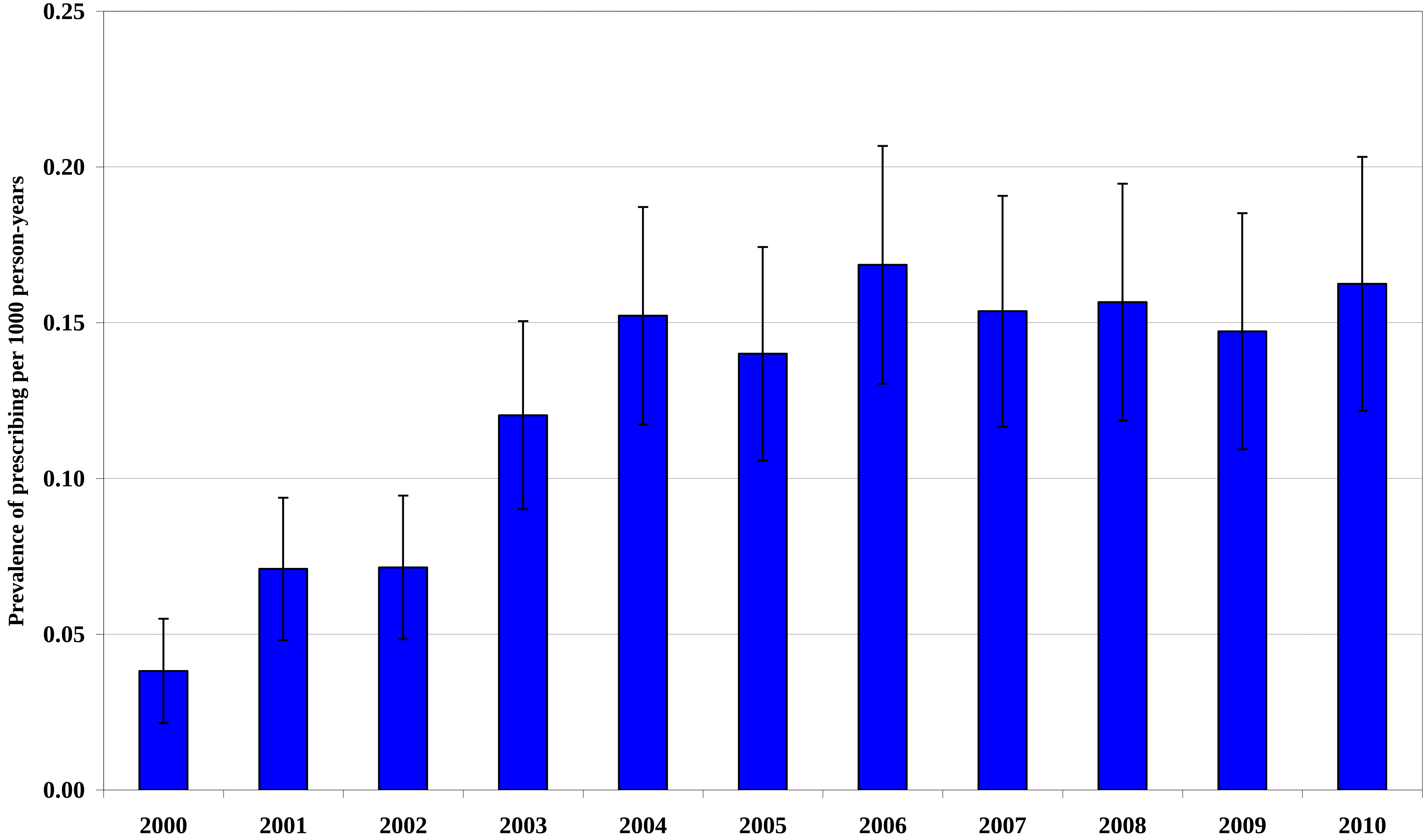


Table 4.8: Total number of patients prescribed metformin for diabetes, polycystic ovarian syndrome (PCOS) and obesity between 2000 and 2010

Diagnosis	Number of patients		
	Boys	Girls	Total
Diabetes only	48	66	114
Obesity only	4	18	22
PCOS and obesity	NA	120	120
Diabetes and obesity	3	8	11
Diabetes, PCOS and obesity	NA	23	23

NA: not applicable

4.3.5.Discussion

This study shows that the overall use of metformin in the paediatric population has steadily increased in primary care, with prescribing prevalence increasing from 0.03 per 1000 person-years in 2000 to 0.16 per 1000 person-years in 2010. This increase was particularly marked amongst girls aged 12-18 years.

There is limited data on paediatric metformin prescribing patterns in the UK. As some prescribing databases do not have links with indications for prescribing, an added strength of this study is that we were able to identify the disease indication for metformin therapy for the majority of patients. However, these findings are subject to some limitations. Firstly, the IMS DA only records prescriptions which issued in primary care and excludes prescriptions issued from hospitals so our data did not include the small number of prescriptions initiated by hospitals. Although the great majority of these would have been continued in primary care and so have been included in our study, unfortunately there are no data to investigate the extent of metformin prescribing in hospitals. Secondly, this study was unable to identify whether subjects were treated with lifestyle modification along with metformin, as healthy diet and exercise are mainstays of treatment for obesity, PCOS and type 2 diabetes (Mastorakos *et al*., 2006; Harwood *et al*., 2007). Thirdly, there was no information on the diagnostic criteria used for any of the conditions we investigated in this study. Diagnoses are often made in secondary care and the IMS DA does not record which criteria have been used to confirm diagnoses in primary care. While diagnostic criteria for type 2 diabetes are internationally accepted, a number of different definitions exist for obesity and PCOS. Fourthly, the IMS DA does not contain data on ethnicity and socioeconomic status, thus their impact on prescribing patterns could not be studied.

The finding that PCOS with obesity was the main indication for metformin prescribing in female adolescents was unexpected. It has been well-documented that adolescent obesity is increasing in population-based studies in the US (Ogden *et al*., 2002) and also in the UK (Viner *et al*., 2009). In addition, a previous study has shown an increased prevalence of type 2 diabetes in adolescents aged 12-18 years in the UK (Hsia *et al*., 2009). Therefore, it is possible that the prevalence of PCOS in adolescents may also have increased. Although metformin has been shown to be of benefit in teenage girls with PCOS in a number of studies (Ibáñez *et al*., 2004; Bridger *et al*., 2006; De Leo *et al*., 2006), a recent RCT did not show benefit of metformin treatment in adolescents (Hoeger *et al*., 2008). Therefore, its efficacy in treating PCOS remains controversial.

There were a small number of patients who received metformin for the treatment of obesity only in this study. In October 2006, in Europe rimonabant was withdrawn due to serious psychiatric adverse reactions. And in January 2010, sibutramine was withdrawn from all markets in the EU due to the risk of adverse cardiovascular events in adults (EMEA 2011). Consequently orlistat is the only licensed anti-obesity drug for use in patients aged over 18 years in the UK (BNF 2011; BNFC 2011; SPC). As there is currently a limited choice of drugs for obesity treatment, metformin may gain in popularity for obesity treatment. A current on-going clinical trial (ClinicalTrials.gov identifier: NCT01487993) has been carried out in the Netherlands to investigate short-term (18 months) and long term (36 months) metformin treatment in obese children and adolescents aged ≥ 10 and ≤ 16. This study is expected to be completed by 2016 (http://clinicaltrials.gov/ct2/show/NCT01487993). Furthermore, a UK-based clinical trial study (ClinicalTrials.gov identifier: NCT01273584) set up to investigate metformin use in obese non-diabetic pregnant women aged 19-50 years (MOP study) is currently recruiting patients. This clinical trial is expected to recruit 850 patients and be completed by 2014. The recruitment of MOP study was completed in July 2015 and there is no result being published at the time of writing this thesis. (http://clinicaltrials.gov/ct2/show/NCT01273584).

After the withdrawal of sibutramine, orlistat is the only drug recommended for obesity treatment in children and adolescents with life-threatening co-morbidities in the NICE guideline (2006). However, gastrointestinal adverse reactions often limit its use. Compared with orlistat, metformin may be an alternative option for obesity treatment as it can improve hyperglycaemia, dyslipidaemia, and weight reduction (Charles *et al*., 2000; Glueck *et al*., 2001). These beneficial effects will consequently reduce the risk of developing diabetes and cardiovascular conditions for obese children and adolescents in adulthood.

4.3.6.Conclusion

Metformin prescribing in children and adolescents for obesity, PCOS or diabetes treatment has increased substantially in the past decade. During this period, the number of teenage girls receiving metformin for PCOS treatment in general practice has increased, although it is not approved for use in this condition. Metformin is only approved for the treatment of type 2 diabetes in children aged over 10 years and in adults. However, its beneficial effects in improving insulin sensitivity and weight loss may increase metformin use for obesity treatment in clinical practice. Currently, the NICE guideline only recommends orlistat for obese children and adolescents (aged ≥ 12 years) with severe co-morbidities. As choice of drug for obesity treatment is limited, metformin use for weight reduction in this population requires further investigation.

Chapter 5 Anti-obesity drug prescribing patterns to obese young people in secondary care in the UK

5.1.The efficacy of metformin on weight reduction in children and adolescents: a systematic review and meta-analysis from randomised controlled trials

5.1.1.Introduction

As discussed earlier (Chapter 1.5.4), a systematic review (Park *et al*., 2009) investigated 5 RCTs on metformin treatment effect in children and adolescents without diabetes aged ≤ 19 years (Freemark *et al*., 2001; Srinivasan *et al*., 2006; Atabek *et al*., 2008; Love-Osbome *et al*., 2008; Yanovski *et al*., 2008). This review showed that metformin reduced BMI by 1.41 kg/m^2 over 6 month's treatment. Since this review was published, new RCTs investigating metformin use in obese children and adolescents have been published in recent years. Therefore, we undertook a systematic review of randomised controlled trials (RCTs) investigating the efficacy of metformin for reducing BMI in obese young people without diabetes.

5.1.2.Aim and objective

Aim: To investigate efficacy of metformin treatment on weight loss in obese young people from RCTs.

Objective: To conduct a systematic review and meta-analysis to investigate metformin efficacy from published RCTs in non-diabetic children and adolescents aged 0-18 years

5.1.3.Methods

5.1.3.1.Literature search

The following databases were searched for RCTs published from January 1996 to February 2014: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). We also searched clinical trial registers: the metaRegister of Controlled Trials (www.controlled-trials.com), WHO clinical trials registry platform (http://www.who.int/ctrp/en) and the US Clinical trials registry (http://www.clinicaltrials.gov/). Hand searching was also carried out to examine the reference lists of the studies identified. Search strategies are presented in Table 5.1.

Table 5.1: Search strategy and search terms in each database

Ovid MEDLINE
1. Metformin or Glucophage or Riomet or Fortamet or Glumetza or Obimet or Dianben or Diabex or Diaformin 2. exp Metformin/ 3. 1 or 2 4. obes$ or obesity 5. Overweight or loss of overweight 6. BMI or Body mass index or Body-mass-index or Weight for height or Weight-for-height or Weight to height ratio or Weight-to-height ratio or Weight height ratio or Weight-height ratio 7. Weight gain or Weight loss or Weight management or Weight maintenance or Weight reduction or Weight decrease or Weight control 8. Waist circumference or Waist measurement 9. Body fat or Body fat percent$ or Percent$ body fat or Fat mass or Adiposity or Body composition 10. Skinfold thickness or skin fold thickness or skin-fold thickness 11. Hyperinsulin or Insulin resistance or metabolic risk or metabolic syndrome 12. Dyslipid?emia or Hyperlipid?emia or Hypercholesterol?emia or Cholesterol or Total cholesterol or Low density lipoprotein cholesterol or LDL cholesterol or High density lipoprotein cholesterol or HDL cholesterol or Triglyceride$ 13. Satiety or Hunger or Appetite or Binge eating 14. ponderal index 15. (adverse effect$ or adverse reaction$ or side effect$).tw. 16. exp Obesity/ 17. body weight changes/ or overweight/ 18. Adipose Tissue/ 19. exp "Body Weights and Measures"/ 20. exp Hyperinsulinism/ 21. exp Dyslipidemias/ 22. exp Appetite/ 23. or/4-22 24. exp Child/ 25. exp Adolescent/ 26. juvenile 27. exp Infant/ 28. child$ 30. infan$ 31. teen$ 32. P?ediatric$ 33. Pediatrics/ 34. or/24-33 35. Randomi#ed controlled trial.pt. 36. exp Randomized Controlled Trial/ 37. exp Random Allocation/ 38. exp Double-Blind Method/ 39. exp Single-Blind Method/ 40. Clinical trial.pt. 41. exp Clinical Trial/ 42. (clinical$ adj5 trial$).tw. 43. (single or double or treble or triple) adj5 (blind$ or mask$) 44. Placebos/ 45. (placebo$ or random$).tw. 46. research design/ 47. Comparative study/ 48. exp evaluation studies/ 49. Follow-up studies/ 50. Prospective studies/ 51. Intention-to-treat.tw. 52. Randomi#ed controlled trial 53. Randomi#ed adj5 controlled

54. or/35-53
55. 34 and 3 and 23 and 54
56. limit 55 to humans

Abbreviations: exp=exploded MeSH term; tw=textword; pt=publication type; adj=adjacency; dollar sign ($), asterisk (*) and percentage sign (%) =unlimited truncation; question mark (?)=optional wildcard.

EMBASE
1. Metformin or Glucophage or Riomet or Fortamet or Glumetza or Obimet or Dianben or Diabex or Diaformin 2. Metformin/ 3. 1 or 2 4. obese or obesity or overweight or adiposity or overeating 5. BMI or Body mass index or Body-mass-index or Weight for height or Weight-for-height or Weight to height ratio or Weight-to-height ratio or Weight height ratio or Weight-height ratio 7. Weight gain or Weight loss or Weight management or Weight maintenance or Weight reduction or Weight decrease or Weight control 8. Waist circumference or Waist measurement 9. (Body adj5 fat) or (Body adj5 fat adj5 percent$) or Percent$ body fat or Fat mass or Adiposity or Body composition 10. Skinfold thickness or (skin adj5 fold adj5 thickness) or skin-fold thickness) 11. waist adj5 hip adj5 ratio 12. Hyperinsulin?emia or insulin resistance or metabolic risk 13. Dyslipid?emia or Hyperlipid?emia or Hypercholesterol?emia or Cholesterol or Total cholesterol or Low density lipoprotein cholesterol or LDL cholesterol or High density lipoprotein cholesterol or HDL cholesterol or Triglyceride$ 14. Satiety or Hunger or Appetite or (Binge adj5 eat$) 15. appetite/ 16. adverse effect$ or adverse reaction$ or side effect$ 17. obesity/ 18. body mass/ 19. body weight/ 20. or/4-19 21. Clinical trial/ 22. Randomized controlled trial/ 23. Randomization/ 24. Single blind procedure/ 25. Double blind procedure/ 26. Crossover procedure/ 27. Placebo/ 28. Randomi?ed controlled trial$.tw. 29. Rct.tw. 30. Random allocation.tw. 31. Randomly allocated.tw. 32. Allocated randomly.tw. 33. (allocated adj2 random).tw. 34. Single blind$.tw. 35. Double blind$.tw. 36. ((treble or triple) adj blind$).tw. 37. Placebo$.tw. 38. Prospective study/ 39. or/21-38 40. child/ 41. adolescent/ 42. pediatrics/ 43. child$ 44. adolescen$ 45. infan$ 46. teen$ 47. p?ediatric$ 48. juvenile 49. or/40-48 50. 39 and 49 and 3 and 20 51. limit 50 to human

Abbreviations: exp=exploded MeSH term; tw=textword; pt=publication type; adj=adjacency; dollar sign ($), asterisk (*) and percentage sign (%) =unlimited truncation; question mark (?)=optional wildcard.

Database	
Cochrane Central Register of Controlled Trials	**metaRegister of Controlled Trials**
“metformin”, AND “**child*, adolescen*, teen*”** AND “**obes*, overweight”** *in* ***Title, Abstract or Keywords***	Metformin AND (child% OR adolescen%) AND (obes% OR overweight)

Abbreviations: exp=exploded MeSH term; tw=textword; pt=publication type; adj=adjacency; dollar sign ($), asterisk (*) and percentage sign (%) =unlimited truncation; question mark (?)=optional wildcard.

5.1.3.2.Eligibility and exclusion criteria

The inclusion criteria for the systematic review were published double-blind randomised RCTs investigating the efficacy of metformin for BMI reduction in young people aged ≤19 years without diabetes, with treatment duration ≥6 months. We excluded quasi-randomised open-label crossover trials and studies those published only in abstract form. There was no restriction on language. Primary outcomes of interest were BMI (kg/m^2) reduction. Secondary outcomes included insulin sensitivity, fasting insulin (μU/mL), homeostatic model assessment insulin resistance (HOMA-IR), fat mass, blood pressure, fasting lipids, and adverse effects.

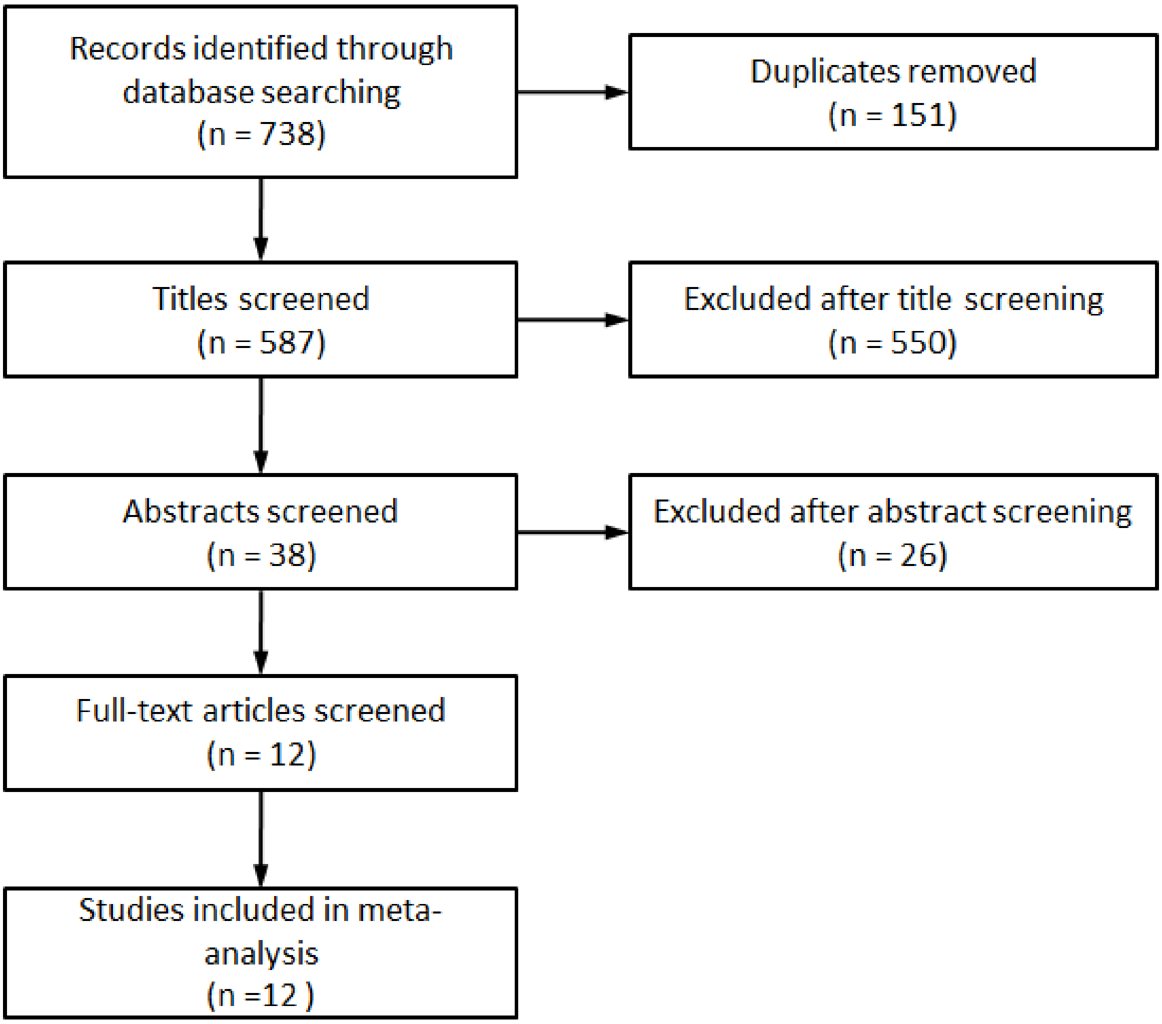
5.1.3.3.Data extraction and quality assessment

Two reviewers performed the electronic searches and screened the articles independently: YF Hsia and MH Park, a research fellow from London School of Hygiene and Tropical Medicine. Articles that clearly did not meet the eligibility criteria were rejected on initial review. Articles marked for potential inclusion were then obtained electronically or in paper copy, and assessed again for inclusion. Disagreements were resolved by discussion until a consensus was reached. The studies that deemed to meet inclusion criteria by both reviewers were included and appraised. The standard form included study design, blinding status, trial duration, mean age of participants, gender, number of participants in treatment and placebo group, interventions and the assessment of intention-to-treat (ITT) analysis. The QUOROM (Quality of Reporting of Meta-analysis) guideline was used for reporting our review.

5.1.3.4.Measures of treatment efficacy and heterogeneity

The primary outcome was expressed as change in BMI (kg/m^2). The weighted mean differences for continuous outcome and risk difference for dichotomous outcomes at the end of study follow-up were calculated. The secondary outcomes of interest included body weight, fat mass, blood pressure, fasting lipids, and adverse effects. Where five or more studies reported a common secondary outcome, treatment effect was assessed in a meta-analysis. To identify the potential causes of the statistical heterogeneity, sensitivity analysis was additionally performed based on the studies' methodological quality. The meta-analysis used a random effects model with RevMan 5.0.16 (Oxford, UK: The Cochrane Collaboration, 2007). The primary outcome analysis was based upon ITT data from the completion of the randomised trial, prior to any cross-over or open-label extension. Where standard deviations (SD) were not reported, these were obtained from standard errors, confidence intervals, *t* values or *P* values that related to the differences between the means in two groups. The DerSimonian and Laird Q test was performed to assess the degree of heterogeneity between studies, and the I^2 statistic was used to determine the percentage of total variation across studies due to heterogeneity.

Figure 5.1: Flow chart of selection and inclusion of papers for systematic review and meta-analysis



5.1.4.Results

The extensive searching identified 738 studies between 1996 and 2013, of which 151 studies were duplicated. A total studies were excluded after the title screening. We went through the abstracts of remaining 38 studies; 26 studies did not meet the inclusion criteria. The most common reasons for exclusion of studies were that the participants' were aged>20 years, or there was a different primary outcome. The full articles of the remaining 12 studies were retrieved (Figure 5.1). All 12 studies met the inclusion criteria (Freemark *et al*., 2001; Srinivasan *et al*., 2006; Love-Osborne *et al*., 2008; Atabek *et al*., 2008; Clarson *et al*., 2009; Wiegand *et al*., 2010; Yanovski *et al*., 2011; Rynders *et al*., 2011; Wilson *et al*., 2012; Mauras *et al*., 2012; Bernadette *et al*., 2012; Kendall *et al*., 2013). Six studies were conducted in the U.S. (Freemark *et al*., 2001; Love-Osborne *et al*., 2008; Rynders *et al*., 2011; Yanovski *et al.*, 2011; Wilson *et al*., 2012; Mauras *et al*., 2012;), and one each in Australia (Srinivasan *et al*., 2006), Germany (Wiegand *et al*., 2010), Chile (Bernadette *et al*., 2012), Canada (Clarson *et al*., 2009), and UK (Kendall *et al*., 2013).

Details of the included studies are shown in Table 5.2. Sample size ranged from 16-120 participants at randomisation. All trials lasted ≥6 months with metformin doses from 1,000-2000 mg/day. Most studies included adolescents; though one US study (Yanovski *et al*., 2011) looked only at younger children (aged 6-12years). Different lifestyle intervention programmes were undertaken such as diet, exercise, goal setting, or motivational support. Two studies did not undertake the lifestyle intervention in either trial arms (Freemark *et al*., 2001; Srinivasan *et al*., 2006). Dosage of metformin varied in the different trials ranging from 1000mg to 2000mg per day. Some studies recruited participants of different ethnicity; in the U.S trials and Australia, most ethnic minorities were African American, Hispanic, or Asian (Freemark *et al*., 2001; Srinivasan *et al*., 2006; Love-Osborne *et al*., 2008; Yanovski *et al*., 2011). Wheras in the UK trial (Kendall *et al*., 2013), the majorityof the participants were white British although 24% wereethnic minorities from British Asian or Afro-Caribbean backgrounds.

The pooled analysis based on 12 studies, there is a statistically significant BMI reduction with metformin treatment compared to placebo of 0.64 kg/m^2; (95% CI: -0.90 to -0.37; n=719) after 6 months use (Figure 5.2). Sensitivity analysis was conducted by removing 2 studies with poorly rated qualities (Rynders *et al*., 2011; Bernadette *et al*., 2012), and the overall estimated effect was -1.25 mg/m^2 (95%CI: -1.90 to -0.61), which remains statistically significant (p<0.0001).

Pooled metformin effect on the homeostasis model assessment of insulin resistance (HOMA-IR) was -0.84 (95% CI: -1.91 to 0.22) (I^2 = 63%; n=592) in 9 studies, but the difference did not reach statistical significance (Figure 5.3). Reduction in fasting insulin was greater in metformin than placebo group in 9 studies, with a reduction of -4.15 µU/mL (95% CI: -7.96 to -0.34) (I^2 = 57%; n=604) (Figure 5.4). Analyses did not provide strong evidence for a treatment effect on weight reduction, fasting glucose, cholesterol, or triglyceride level (Figure 5.5-5.8). Pooled metformin effect on HDL was 0.15 (95% CI: -0.07 to 0.38) (I^2 = 97%; n=640), and -0.03 (95% CI: -0.08 to 0.02) (I^2 = 33%; n=526) if the US study by Freemark (2001) (outlier result) was excluded (Figure 5.9).

Gastrointestinal problems (diarrhoea, nausea, and abdominal pain) were the most commonly reported adverse events and were more frequently reported in the metformin than in the placebo group. Two studies reported gastrointestinal problems as the reason for participants leaving studies (Love-Osborne *et al*., 2008; Wiegand *et al*., 2010). In addition to gastrointestinal adverse events, the German study also reported unspecific events such as weakness or fatigue for a short time though with spontaneous remission in both the metformin (n=3) and placebo (n=4) groups (Wiegand *et al*., 2010).

Table 5.2: Summary of randomised controlled trials (RCT) of metformin use for obese non-diabetic young people aged ≤19

Study	Country	No of patients[†]	Age (years)	Length of treatment	Daily dose (mg)	Outcomes	Lifestyle intervention
Atabek *et al*. 2008	Turkey	120 (metformin: 90; placebo: 30)	9-17	6 months	500mg x 2	Reduction in BMI of 2.7kg/m^2 in metformin group.	Diet, exercise, behavioural therapy tailored for individual patients
Clarson *et al*. 2009	Canada	25 (metformin: 11; placebo: 14)	10-16	6 months	500mg x 3	Reduction in BMI of 1.8kg/m^2 in metformin with lifestyle intervention group. Increased in BMI of 0.5 kg/m^2 in lifestyle intervention only group.	Lifestyle intervention (nutritional and exercise education and motivational support)
Freemark *et al.* 2001	US	29 (metformin: 14: placebo: 15)	12-19	6 months	500mg x 2	Reduction in BMI of 0.5 kg/m^2 with metformin treatment. BMI was increased of 0.9 kg/m^2 in placebo group.	No lifestyle intervention
Love-Osborne *et al.* 2008	US	85 (metformin: 60; placebo: 25)	12-19	6 months	850mg x 2	Overall, there was no difference in BMI change; girls who have better adherence on metformin treatment with significant different	Lifestyle intervention (personal goal setting).
Srinivasan *et al.* 2006	Australia	22 (Metformin: 10; placebo: 12)	9-18	6 months	1000mg x 2	Reduction in BMI of 1.26kg/m^2 and weight by 4.35kg in metformin group.	No lifestyle intervention
Yanovski *et al*. 2011	US	100 (Metformin: 45; placebo: 40)	6-12	open-label metformin treatment (months 7-12)	1000mg x 2	Reduction in weight of 3.38kg, and a reduction in BMI of 1.09kg/m^2 in metformin group.	Lifestyle intervention,

Abbreviation: BMI: body mass index; BMI SDS: BMI Standard Deviation Score. . HOMA-IR: homeostatic model assessment insulin resistance. [*]Studies not included in Park *et al.* review paper. [†]No. of patients were those patients included in the final analysis in each study.

Continued

Study	Country	No of patients†	Age (years)	Length of treatment	Daily dose	Outcomes	Lifestyle intervention
Wiegand *et al.* 2010	Germany	70 (metformin:36; placebo: 34)	12-18	6 months	500mg x 2	No significant reduction in BMI in metformin group	Lifestyle intervention
Rynders *et al*. 2011	US	16 (metformin:9; placebo:7)	14.3±2.4	6 months	500mg x 2 (<12 years) 1000mg x 2 (≥12 years)	Reduction in BMI of 1.7kg/m^2 with metformin and lifestyle intervention	Lifestyle intervention (diet or exercise)
Wilson *et al*. 2012 (Glaser Pediatric Research Network)	US	77 (metformin: 39; placebo:38)	13-18	48 weeks	2000mg	Reduction in BMI of 0.9 kg/m^2 with metformin and lifestyle intervention Reduction in BMI of 0.2 kg/m^2 with lifestyle intervention only	Lifestyle intervention
Mauras *et al*. 2012	US	42 (metformin: 23; placebo:19)	8-17		500mg x 2 (<12 years) 1000mg x 2 (≥12 years)	Reduction in BMI of 2.4 kg/m^2 with metformin and lifestyle intervention Reduction in BMI of 1.1 kg/m^2 with lifestyle intervention only	Lifestyle intervention (diet or exercise)
Bernadette *et al*. 2012	Chile	19 (metformin: 10; placebo:9)	13-19	6 months	500 mg extended release daily	Reduction in BMI of 1.85 kg/m^2 with metformin and lifestyle intervention Reduction in BMI of 1.5 kg/m^2 with lifestyle intervention only	Lifestyle intervention
Kendall *et al*. 2013 (MOCA trial)	UK	151 (Metformin :74; Placebo: 77)	8-18	6 months	1500mg	Reduction in BMI of 0.25kg/m^2 with metformin and lifestyle intervention Increased in BMI of 0.21 in placebo group	Lifestyle intervention (diet and exercise advice)

Abbreviations: BMI, body mass index; BMI SDS, BMI Standard Deviation Score; HOMA-IR, homeostatic model assessment insulin resistance; MOCA, Metformin in Obese Children and Adolescents.†No. of patients were those patients included in the final analysis in each study.

Figure 5.2: Forest plot comparing change in BMI (kg/m2) in metformin and placebo groups

	Metformin			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Atabek 2008	-2.08	2.32	90	0.65	2.5	30	10.6%	-1.15 [-1.59, -0.71]
Bernadette 2012	-1.85	1.77	10	-1.5	1.63	9	5.5%	-0.20 [-1.10, 0.71]
Clarson 2009	-1.8	2.65	11	0.5	1.12	14	5.8%	-1.15 [-2.01, -0.28]
Freemark 2001	-0.5	0.71	14	0.9	1.33	15	6.3%	-1.26 [-2.07, -0.46]
Kendall 2013	-0.25	1.77	74	0.21	1.63	77	12.2%	-0.27 [-0.59, 0.05]
Love-Osborne 2008	-0.16	1.89	48	0.63	1.29	16	8.8%	-0.44 [-1.01, 0.13]
Mauras 2012	-2.4	2.4	23	0.2	2.6	19	7.9%	-1.02 [-1.67, -0.37]
Rynders 2011	-1.7	1.77	9	0	1.63	7	4.5%	-0.94 [-2.00, 0.12]
Srinivasan 2006	-1.26	1.68	22	0	1.68	22	8.3%	-0.74 [-1.35, -0.12]
Wiegand 2010	0.07	1.77	36	-0.21	1.63	34	10.2%	0.16 [-0.31, 0.63]
Wilson 2012	-0.9	2.6	27	0.2	2.6	27	9.2%	-0.42 [-0.96, 0.12]
Yanovski 2011	-0.78	1.31	45	0.32	1.64	40	10.6%	-0.74 [-1.18, -0.30]
Total (95% CI)			**409**			**310**	**100.0%**	**-0.64 [-0.90, -0.37]**

Heterogeneity: Tau² = 0.12; Chi² = 28.27, df = 11 (P = 0.003); I² = 61%

Test for overall effect: Z = 4.66 (P < 0.00001)

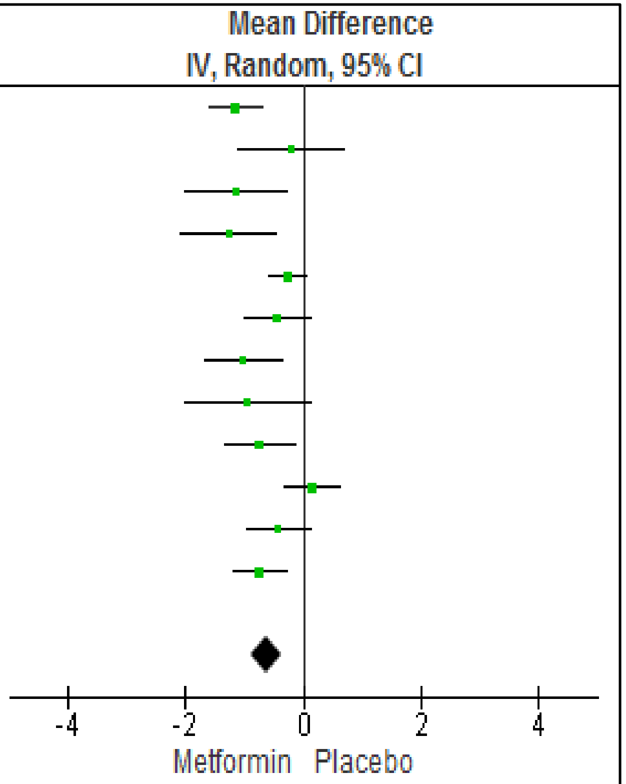


Figure 5.3: Forest plot comparing change in homeostasis model assessment of insulin resistance (HOMA-IR)

	Metformin			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Atabek 2008	-3.74	3.8	90	-1.05	2.3	30	16.1%	-2.69 [-3.83, -1.55]
Clarson 2009	-0.88	3.62	11	-2.53	3.82	14	7.9%	1.65 [-1.28, 4.58]
Freemark 2001	-3.08	3.83	14	-0.08	6.59	15	5.4%	-3.00 [-6.89, 0.89]
Kendall 2013	0.2	3.63	74	0.29	3.75	77	15.9%	-0.09 [-1.27, 1.09]
Mauras 2012	0.34	3.64	23	1.6	3.49	19	10.9%	-1.26 [-3.42, 0.90]
Rynders 2011	-0.2	3.63	9	2.5	3.75	7	5.9%	-2.70 [-6.35, 0.95]
Wiegand 2010	-0.55	3.63	36	-1.05	3.75	34	13.0%	0.50 [-1.23, 2.23]
Wilson 2012	-0.1	4.16	27	-0.8	3.64	27	11.2%	0.70 [-1.39, 2.79]
Yanovski 2011	0.68	3.7	45	2.23	3.89	40	13.6%	-1.55 [-3.17, 0.07]
Total (95% CI)			**329**			**263**	**100.0%**	**-0.84 [-1.91, 0.22]**

Heterogeneity: Tau² = 1.49; Chi² = 21.70, df = 8 (P = 0.005); I² = 63%

Test for overall effect: Z = 1.56 (P = 0.12)

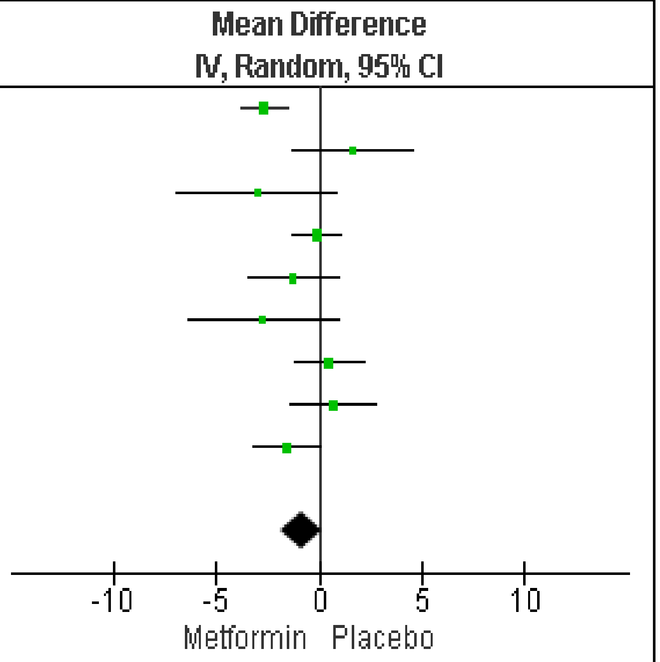


Figure 5.4: Forest plot comparing change in fasting insulin (μU/mL) in metformin and placebo groups

	Metformin			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Atabek 2008	-14.6	12.1	90	-4	9.2	30	19.9%	-10.60 [-14.73, -6.47]
Clarson 2009	-3.6	14.59	11	-9.4	15.34	14	7.5%	5.80 [-5.99, 17.59]
Freemark 2001	-12.3	15.28	14	-1.6	30.16	15	4.1%	-10.70 [-27.93, 6.53]
Kendall 2013	-0.65	21.15	74	3.77	23.09	77	13.8%	-4.42 [-11.48, 2.64]
Love-Osborne 2008	-2.42	26.57	48	-6.56	26.57	16	5.1%	4.14 [-10.89, 19.17]
Rynders 2011	-0.7	21.15	9	13.3	23.09	7	2.7%	-14.00 [-35.99, 7.99]
Srinivasan 2006	-2.2	3.7	22	0	3.7	22	24.0%	-2.20 [-4.39, -0.01]
Wiegand 2010	-4.5	21.15	36	-5.4	23.09	34	8.9%	0.90 [-9.49, 11.29]
Yanovski 2011	3.24	15.74	45	9	16.63	40	14.0%	-5.76 [-12.67, 1.15]
Total (95% CI)			**349**			**255**	**100.0%**	**-4.15 [-7.96, -0.34]**

Heterogeneity: Tau² = 14.48; Chi² = 18.64, df = 8 (P = 0.02); I² = 57%
Test for overall effect: Z = 2.14 (P = 0.03)

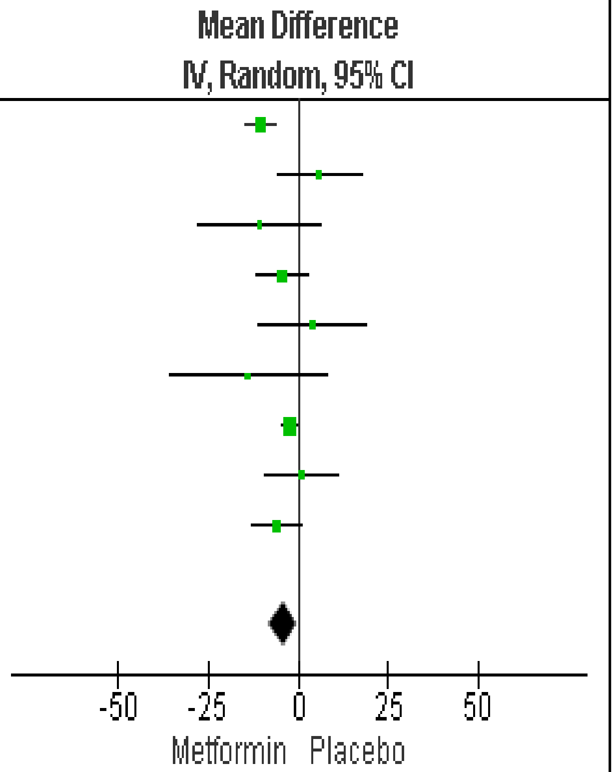


Figure 5.5: Forest plot comparing body weight (kg) change in metformin and placebo groups

	Metformin			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Atabek 2008	-3.4	9.48	90	3.6	10.94	30	18.3%	-7.00 [-11.38, -2.62]	
Kendall 2013	2.4	7.12	74	0.4	7.4	74	24.2%	2.00 [-0.34, 4.34]	
Mauras 2012	-4.9	4.8	23	-1.7	4.79	19	22.6%	-3.20 [-6.11, -0.29]	
Rynders 2011	-5.1	7.12	9	-3	7.4	7	11.6%	-2.10 [-9.29, 5.09]	
Yanovski 2011	1.47	6.08	45	4.85	6.47	40	23.3%	-3.38 [-6.06, -0.70]	
Total (95% CI)			**241**			**170**	**100.0%**	**-2.55 [-5.75, 0.65]**	

Heterogeneity: Tau² = 9.56; Chi² = 17.78, df = 4 (P = 0.001); I² = 77%

Test for overall effect: Z = 1.56 (P = 0.12)

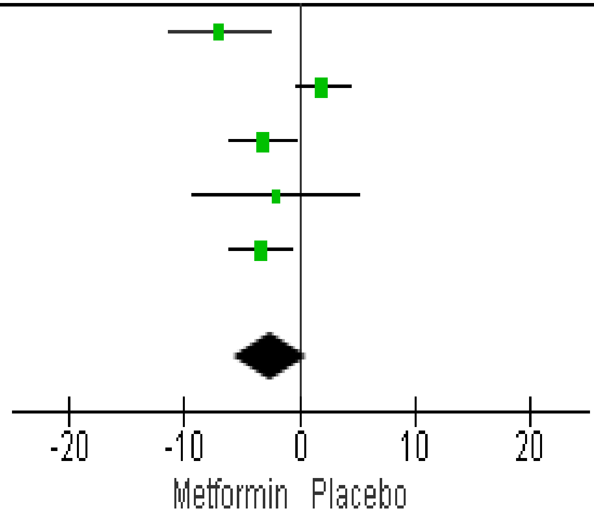


Figure 5.6: Forest plot comparing fasting glucose (mmol/litre) change in metformin and placebo groups

	Metformin			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Atabek 2008	-0.13	0.95	90	-0.23	0.66	30	18.7%	0.10 [-0.21, 0.41]
Clarson 2009	0.3	2.22	11	-0.1	2.22	14	3.9%	0.40 [-1.35, 2.15]
Freemark 2001	-0.54	0.77	14	0.28	0.55	15	15.7%	-0.82 [-1.31, -0.33]
Kendall 2013	-0.04	2.22	74	0.01	2.22	77	12.3%	-0.05 [-0.76, 0.66]
Love-Osborne 2008	0.07	0.77	48	-0.17	0.47	16	18.5%	0.24 [-0.08, 0.56]
Rynders 2011	-0.9	2.22	9	-3.4	2.22	7	2.6%	2.50 [0.31, 4.69]
Srinivasan 2006	-0.2	0.44	22	0	0.44	22	19.4%	-0.20 [-0.46, 0.06]
Wiegand 2010	0.6	2.22	36	2	2.22	34	8.2%	-1.40 [-2.44, -0.36]
Yanovski 2011	-0.88	10.03	45	3.47	10.79	40	0.7%	-4.35 [-8.80, 0.10]
Total (95% CI)			**349**			**255**	**100.0%**	**-0.18 [-0.56, 0.21]**

Heterogeneity: Tau² = 0.18; Chi² = 30.13, df = 8 (P = 0.0002); I² = 73%
Test for overall effect: Z = 0.90 (P = 0.37)

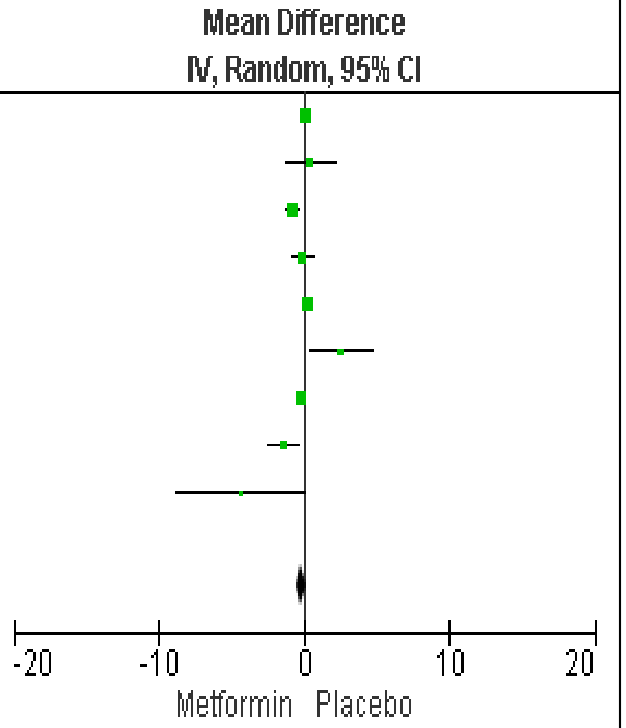
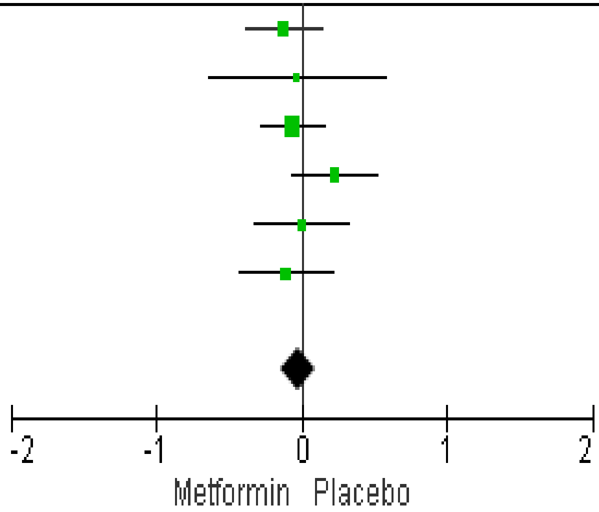


Figure 5.7: Forest plot comparing cholesterol (mmol/litre) change in metformin and placebo groups

	Metformin			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Atabek 2008	-0.31	0.85	90	-0.19	0.54	30	21.0%	-0.12 [-0.38, 0.14]	
Freemark 2001	-0.21	0.64	14	-0.18	1	15	3.9%	-0.03 [-0.64, 0.58]	
Kendall 2013	-0.06	0.66	74	0	0.7	77	30.4%	-0.06 [-0.28, 0.16]	
Mauras 2012	0.03	0.48	23	-0.2	0.48	19	16.8%	0.23 [-0.06, 0.52]	
Wiegand 2010	-0.2	0.66	36	-0.2	0.7	34	14.0%	0.00 [-0.32, 0.32]	
Yanovski 2011	-0.23	0.8	45	-0.12	0.71	40	13.9%	-0.11 [-0.43, 0.21]	
Total (95% CI)			**282**			**215**	**100.0%**	**-0.02 [-0.14, 0.10]**	



Heterogeneity: Tau² = 0.00; Chi² = 3.83, df = 5 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)

Figure 5.8: Forest plot comparing triglycerides (mmol/litre) change in metformin and placebo groups

	Metformin			Placebo				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Atabek 2008	-0.7	1.01	90	-0.2	0.62	30	12.4%	-0.50 [-0.80, -0.20]
Clarson 2009	-0.38	0.56	11	0.19	0.79	14	7.3%	-0.57 [-1.10, -0.04]
Freemark 2001	-0.02	0.43	14	-0.15	0.53	15	11.2%	0.13 [-0.22, 0.48]
Kendall 2013	-0.14	0.72	74	-0.24	0.69	77	14.8%	0.10 [-0.13, 0.33]
Love-Osborne 2008	0.09	1.1	48	-0.45	0.89	16	7.2%	0.54 [0.00, 1.08]
Mauras 2012	-0.03	0.43	23	0	0.39	19	14.1%	-0.03 [-0.28, 0.22]
Wiegand 2010	-0.03	0.72	36	0.17	0.69	34	11.7%	-0.20 [-0.53, 0.13]
Wilson 2012	-0.02	0.73	27	0.01	0.73	27	10.2%	-0.03 [-0.42, 0.36]
Yanovski 2011	0.09	0.79	45	0.04	0.85	40	11.2%	0.05 [-0.30, 0.40]
Total (95% CI)			**368**			**272**	**100.0%**	**-0.06 [-0.24, 0.12]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 20.60$, $df = 8$ ($P = 0.008$); $I^2 = 61\%$

Test for overall effect: $Z = 0.66$ ($P = 0.51$)

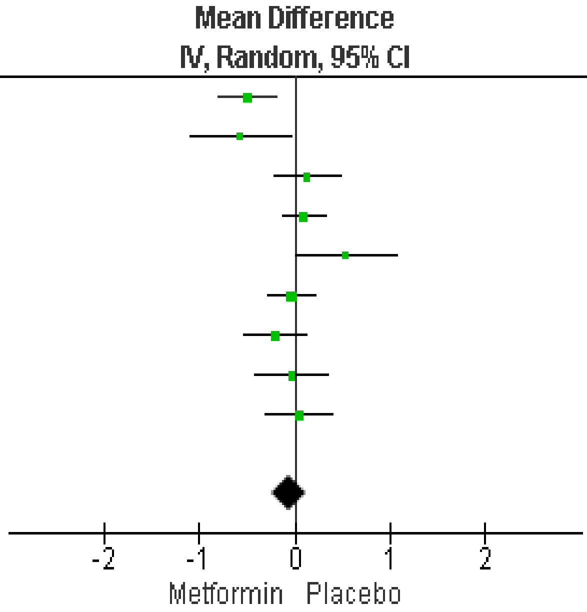
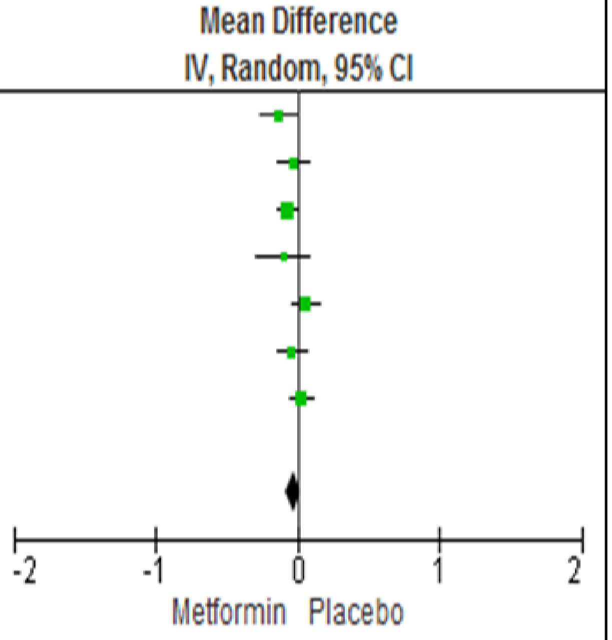


Figure 5.9: Forest plot comparing HDL (mmol/liter) change in metformin and placebo groups

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Atabek 2008	0.04	0.3	90	0.17	0.35	30	9.6%	-0.13 [-0.27, 0.01]
Clarson 2009	0.09	0.1	11	0.12	0.19	14	12.7%	-0.03 [-0.15, 0.09]
Kendall 2013	0.05	0.23	74	0.12	0.23	77	22.3%	-0.07 [-0.14, 0.00]
Love-Osborne 2008	-0.03	0.41	48	0.07	0.3	16	5.9%	-0.10 [-0.29, 0.09]
Mauras 2012	0.09	0.14	23	0.03	0.17	19	16.5%	0.06 [-0.04, 0.16]
Wiegand 2010	-0.02	0.23	36	0.02	0.23	34	14.1%	-0.04 [-0.15, 0.07]
Wilson 2012	0.03	0.16	27	0	0.16	27	18.9%	0.03 [-0.06, 0.12]
Total (95% CI)			**309**			**217**	**100.0%**	**-0.03 [-0.08, 0.02]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.95$, df = 6 (P = 0.18); $I^2 = 33\%$

Test for overall effect: Z = 1.12 (P = 0.26)



5.1.5.Discussion

In this updated systematic review and meta-analysis, 12 RCTs on metformin treatment in non-diabetic obese children and adolescents were included in the analysis. Compared with placebo, metformin reduced BMI by 0.64 kg/m^2 (95% CI: -0.90 to -0.37) in this population. Fasting insulin was improved in the metformin-treated obese young people compared to those treated with placebo, with a reduction of 4.15 µU/ml (95% CI: -7.96 to -0.34), and no statistically significant heterogeneity amongst individual studies. Also there was a reduction of HOMA-IR in metformin treated obese young people [-0.84 (95% CI: -1.91 to 0.22)] compared with the placebo group. There were no serious adverse reactions reported in any of the included studies. The most commonly reported adverse events were gastrointestinal problems.

Comparison with other reviews

This review included more trials and is current as of February 2014; the findings were consistent with previously published review that demonstrated a short-term metformin treatment effects on BMI reduction in non-diabetic obese young people. Whereas a previous meta-analysis of three studies reported no statistically significant change in BMI reduction in patients receiving metformin after 6 months [-0.17 kg/m^2 (95% CI: -0.62 to -0.28)] (McGovern *et al*., 2008). It needs to be addressed that the trials included in McGovern and colleagues systematic review ranging from 8-week trial (Kay *et al*., 2001) to 6-month trial (Freemark *et al*., 2001; Srinivasan *et al*., 2006). Another meta-analysis of five studies reported that metformin reduced BMI by 1.42 kg/m^2 (95% CI: 0.83 to 2.02) after 6 months of treatment (Park *et al*., 2009). The most recent systematic review and meta-analysis study which included 8 trials, which show a statistically significant BMI reduction by 1.40 mg/m^2 (95% CI: -1.98 to -0.81) in the metformin-treated group after 6 months treatment (McDonagh *et al*., 2014). However, this recent review study only included studies published from 1996 to December 2012, so it was not included in the MOCA trial in UK (Kendall *et al*., 2013) and a RCT trial in Chile (Bernadette *et al*., 2012). When compared with orlistat a drug that is currently licensed for obesity, metformin has a smaller effect: meta-analysis of RCTs of orlistat reported an effect of -0.83 kg/m^2 (95%CI: -0.47 to -1.9) after 6 months of treatment (Viner *et al*., 2009). Also metformin may not be as effective as behaviour interventions in reducing BMI in obese young people as a Cochrane review which included 64 RCTs (5,230 participants) reported a BMI reduction of 3.04 kg/m^2 (95% CI: -3.14 to -2.94) at 6 months with behavioural interventions alone in obese adolescents and this was maintained at 12 months follow-up (Oude *et al*., 2009).

Strengths and limitations

A rigorous systematic review and meta-analysis was undertaken using 2 independent reviewers adhering to the established Cochrane Collaboration methodology. In addition, we included more recent trials in our review compared to a previous study which analysed only 5 RCTs in the review (Park *et al*., 2009). However, our findings have several limitations which should be noted. Firstly, there was moderate and significant statistical heterogeneity between studies for several of the metabolic parameters (e.g. HOMA-IR, fasting insulin, fasting glucose, HDL, triglycerides). It is likely that this heterogeneity is the result of differences in co-interventions and participants from different ethnic backgrounds (e.g. African American, Hispanic, Asian, Afro-Caribbean). The issue of heterogeneity between studies has been addressed in previous reviews (Bouza *et al*., 2012; McDonagh *et al*., 2014). Several sensitive analyses were performed in these two review studies but the cause of the heterogeneity remains unclear (Bouza *et al.*, 2012). However, the reviewers did not have access to individual patient data to investigate the cause of this heterogeneity. Secondly, all trials that were included were conducted in s specialist care setting, so the generalisability of these findings to the general population remains unclear. Also, the participants included in the trials were very carefully selected obese young people, the results of which are difficult to extrapolate to other populations. Thirdly, we only analysed data that were extractable from the publications of the studies and this may be a source of bias as studies may have only published secondary outcomes that differed significantly from the placebo. Fourthly, there was an absence of specific results such as sex, ethnic group, or socioeconomic level in individual studies. Therefore, we were unable to conduct stratified analyses based on these variables, which may have affected metformin treatment outcomes.

5.1.6. Conclusion

Compared to placebo, metformin caused a decrease in BMI by 0.64 mg/m^2 in non-diabetic obese young people from short-term RCTs after 6 months of treatment. Metformin may be efficacious in reducing BMI amongst obese children and adolescents in short-term RCT. However, this treatment effect may not be clinically relevant in terms of improving cardiovascular risk for obese young people. Further, RCTs with longer treatment periods and larger sample sizes are needed. In addition, it is difficult to extrapolate findings from RCTs to real-life clinical practice. Therefore, we conducted a prospective cohort study in a regional paediatric clinic to investigate the effect of metformin on weight loss in obese young people.

5.2. Drug prescribing patterns for obesity treatment in young people: experience in a regional paediatric weight management clinic

5.2.1. Introduction

As discussed in Chapter 1, the 2006 NICE guidelines recommended that drug treatment for obesity should be initiated by a specialist at a secondary care clinic, for children and adolescents aged ≥12 years, with life-threatening co-morbidities or severe psychological co-morbidities. However, there is currently no published evidence on drug use for obesity treatment initiated in secondary care in the UK. Therefore, a cohort study was conducted to investigate drug prescribing patterns for obesity treatment at a regional paediatric weight management clinic.

5.2.2. Aim and objectives

A retrospective cohort study to determine the effect of metformin treatment on weight status in obese young people aged 10-18 years treated in a paediatric weight management clinic in the UK National Health Service (NHS). The specific objective was to compare BMI, BMI standard deviation score (SDS), and weight change for obese patients who received metformin with lifestyle intervention (exercise advice and healthy eating) to patients who received lifestyle intervention alone after 6 months of treatment.

5.2.3. Methods

5.2.3.1. Data collection and handling

Data were retrospectively collected at a paediatric weight management clinic at UCLH between January 2007 and December 2010. Data collection was conducted by two final year pharmacy students, Reema Patel and Iao Choe Lei, from the Centre for Paediatric Pharmacy Research (CPPR), UCL School of Pharmacy (previously known as the School of Pharmacy, University of London). As this study involved accessing patients' clinical records which could be considered a violation of patient confidentiality, if undertaken by non-UCLH staff, both pharmacy students had an honorary contract approved from UCLH before commencing data collection. Patients' data were only accessed within UCLH premises under the supervision of Dr Billy White[3] and the investigator.

Information was mainly obtained from the Clinical Data Repository (CDR) which is a form of electronic medical records consisting of information that includes a patient identifier, the

[3] Dr.Billy White-Clinical Research Fellow at University College London Hospital.

patient's date of birth, postcode, demographic information (e.g. sex, ethnicity), medical treatment, out-patient appointments, and clinical correspondence related to all patients under the care of UCLH. At each clinic appointment, patients attending the paediatric weight management clinic had their weight and height measured by nurses and these measurements were recorded in paper-based medical records. All obese patients who attended the paediatric weight management clinic at UCLH were given lifestyle intervention, including advice on exercise and on healthy eating from a dietician (lifestyle intervention). In addition to lifestyle intervention for managing obesity, other treatment options would also be discussed with patients and their families based on each patient's medical and psychological conditions. For those patients with significant morbidities, drug treatment (e.g. orlistat, sibutramine) would be prescribed together with lifestyle intervention. Insulin resistance was measured using oral glucose tolerance test (OGTT) at the clinic. For patients with insulin resistance syndrome, metformin was prescribed together with lifestyle intervention (Viner & Nicholls, 2005). However, data on insulin resistance were not available in this analysis. After the completion of each clinic visit, medical doctors summarised the consultation and wrote a letter to each patient's GP (which included the patients' height and weight). These letters were also available on the CDR. In the CDR database, ethnicity was grouped into six categories: White British, Black, Asian, mixed, other ethnic group, and not stated.

Each patient's postcode was mapped to the Index of Multiple Deprivation 2007 (IMD) (http://www.communities.gov.uk/documents/communities/pdf/576659.pdf) using the Geographical Information System (GIS) methods for individual patients (http://geoconvert.mimas.ac.uk/index.htm). Detailed information on the IMD domain indicators are provided in Appendix 11. The steps to obtaining IMD are presented in Appendix 12. The IMD is the UK Government's official measure of deprivation on a small area level, which is widely used as the current standard measure of deprivation (Jordan *et al*., 2004). The IMD is based on information from seven domain indicators: income, employment, health and disability, education, skills and training, barriers to housing and services, crime, and living environment (http://www.communities.gov.uk). The IMD assigns a score of overall deprivation based on the characteristics of a geographical unit called Super Output Area (SOA) (http://www.communities.gov.uk).

There are three layers of SOA: lower layer, middle layer and upper layer. The middle Supper Output Area (SOA) and the upper SOA tend to have diverse populations as the data analysed are from larger areas. The Office for National Statistic (ONS) has decided that there was not enough interest to generate the upper SOA data (http://www.ons.gov.uk/ons/index.html). In this study, the Lower SOA (LSOA) was used. The advantage of using the LSOA is that population data and deprivation scores are obtained from the smallest area, and populations will be more homogeneous in small areas and have similar levels of deprivation. LSOA can then be grouped into deprivation deciles (10 groups) or quintiles (5 groups). Compared to quintiles the deciles give a more precise picture of deprivation and are more useful for further inequalities analysis as the larger number of groupings provides a more accurate indication of deprivation. The ten deciles of the IMD are given below:

1. Most deprived (Decile 1) : IMD rank between 1 and 3248
2. Second most deprived (Decile 2): IMD rank between 3249 and 6496
3. Third most deprived (Decile 3): IMD rank between 6497 and 9745
4. Fourth most deprived (Decile 4): IMD rank between 9746 and 12993
5. Fifth most deprived (Decile 5): IMD rank between 12994 and 16241
6. Sixth most deprived (Decile 6): IMD rank between 16242 and 19489
7. Seventh most deprived (Decile 7): IMD rank between 19490 and 22737
8. Eighth most deprived (Decile 8): IMD rank between 22738 and 25986
9. Ninth most deprived (Decile 9): IMD rank between 25987 and 29234
10. Least deprived (Decile 10): IMD rank between 29235 and 32482

BMI was calculated using the formula: weight in kilograms divided by the square of height in meters (kg/m^2). The BMI Standard Deviation Score (SDS) was calculated from weight and height by adjusting for age and gender by using British 1990 reference data (Cole *et al*., 1995). The ImsGrowth programme was used for BMI SDS calculation (http://homepage.mac.com/tjcole). The ImsGrowth programme is a Microsoft Excel "add-in programme" using Excel 2000 with Visual Basic for Application (VBA). This programme was designed to analyse the growth data according to age and sex, and it was developed by Professor Tim Cole at UCL Institute Child Health.[4]

For each individual patient, a unique identification code was allocated to provide anonymity. Data were inputted into a Microsoft Excel spread sheet (Microsoft Corporation, Washington, US) during data collection. The excel spread sheet was then imported into Stata/MP 11 (StataCorp, College Station, Texas, US) for data cleaning purposes. The

[4]ImsGrowth is available to be downloaded from http://www.healthforallchildren.co.uk/.

dataset for analysis was stored on a secure sever at CPPR and it was only made available to the main researcher-Yingfen Hsia, who analysed the data.

5.2.3.2.Statistical analysis

The results were analysed using descriptive statistics, by use of Stata/MP software. Frequency of results was analysed using cross tabulation.

5.2.4.Ethical considerations

This study was a service evaluation to investigate drug prescribing to young people at the UCLH paediatric weight management clinic. Ethical approval was granted by UCL School of Pharmacy Ethics Research Committee (Appendix 10). Approval for the study was sought and received from, Professor Russell Viner at the UCLH paediatric weight management clinic.

5.2.5.Results

A total of 1,231 clinic appointments were captured for 301 patients (57% girls; n=173) aged 10-18 years during the 4-year study period, with a median number of clinic appointments per patient of 3 (interquartile range 4). Table 5.3 shows the baseline characteristics of the whole study population by gender. The overall mean age of the study population was 14.2±2.2 years at baseline (14.3±2.1 years for boys and 14.1±2.2 years for girls). Ethnicity had been recorded for 272 patients but for 29 patients their ethnicity was recorded as "not stated". One hundred and eighty patients (180/301; 59.8%) were White British, 36 patients (36/301; 11.2%) were Black (e.g. African, Caribbean, other Black), 27 (27/301; 8.9%) patients were Asian (e.g. Pakistani, Indian, Bangladeshi, other Asian), 22 (22/301; 7.3%) were mixed race, and 7 (7/301; 2.3%) were from other ethnicities. The overall mean BMI (with standard deviation; SD) at baseline was 36.9±8.2 kg/m^2 and the overall mean BMI SDS was 3.3±0.8. In boys, the mean BMI at baseline was 37.7±8.5 and 36.5±7.9 in girls. The mean BMI SDS at baseline was 3.4±0.6 and 3.2±0.8 in boys and girls, respectively.

Metformin was the drug most frequently prescribed for obesity treatment in both sexes. A total of 183 (60.7%; 183/301) patients in the study population had received a drug for obesity treatment during the study period. Of these, 166 (90.7%; 166/183) patients had received metformin. The number of patients who received orlistat and/or sibutramine for treatment was relatively low (Table 5.1). Based on the IMD score of LSOA, most patients were living in the most deprived areas (decile 1 and decile 2) compared to living in the least deprived area (decile 10).

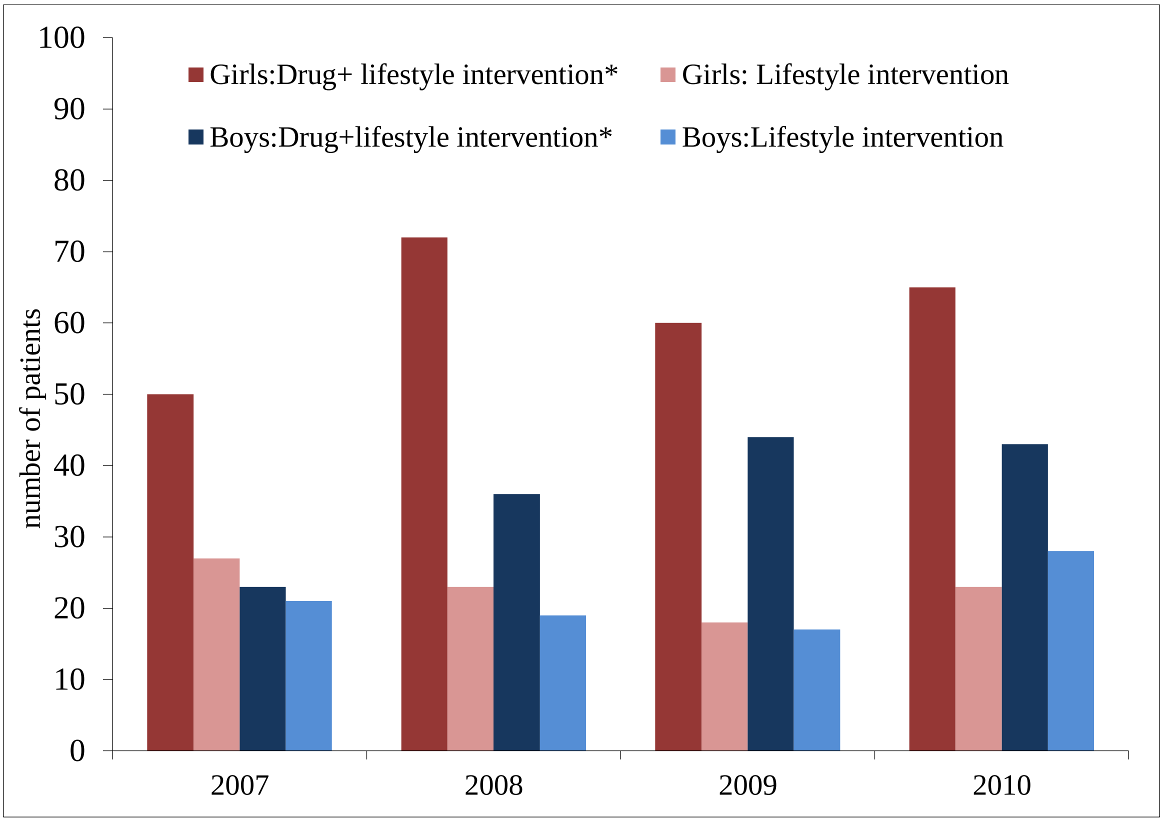
Table 5.3: Baseline characteristics of study cohort (aged 10-18 years) between 2007 and 2010 at the UCLH paediatric weight management clinic

	Boys	Girls	Total
Number of patients (%)	128	173	301
Age (year)	14.3±2.1	14.1±2.2	14.2±2.2
Ethnicity % (n)			
British White	60.2 (77)	59.5 (103)	59.8 (180)
*Black**	11.7 (15)	12.1 (21)	11.9 (36)
Asian†	7.0 (9)	10.4 (18)	8.9 (27)
Mixed	7.0 (9)	7.5 (13)	7.3 (22)
Other ethnic group	0.8 (4)	1.7 (3)	2.3 (7)
Not stated	10.9 (14)	8.7 (15)	9.6 (29)
Weight (kg) *(n=285)*	106.1±29.9	96.4±25.7	100.5±27.9
Height (cm) *(n=285)*	167.0±12.5	161.8±9.5	164.0±11.2
BMI (kg/m^2) *(n=285)*	37.7±8.5	36.5±7.9	36.9±8.2
BMI SDS *(n=285)*	3.4±0.6	3.2±0.8	3.3±0.8
BP *(n=202)*			
Systolic BP (mmHg)	129.1±13.9	125.7±16.2	127.0±15.4
Diastolic BP (mmHg)	73.3±9.0	71.1±9.5	72.0±9.4
Anti-obesity drug treatment‡ % (n)			
(n=183; 112 girls and 71 boys)			
Orlistat	7.0 (5)	13.4 (15)	10.9 (20)
Sibutramine	11.3 (8)	14.3 (16)	13.1 (24)
Metformin	93.0 (66)	89.3 (100)	90.7 (166)
IMD 2007 decile % (n)			
(n=273)			
Decile 1(Most deprived)	19.3 (23)	11.0 (17)	14.7 (40)
Decile 2	28.6 (34)	20.8 (32)	24.2 (66)
Decile 3	10.9 (13)	21.4 (33)	16.9 (46)
Decile4	12.6 (15)	11.0 (17)	11.7 (32)
Decile 5	5.0 (6)	8.4 (13)	7.0 (19)
Decile6	7.6 (9)	6.5 (10)	7.0 (19)
Decile 7	3.4 (4)	7.8 (12)	5.9 (16)
Decile 8	4.2 (5)	4.6 (7)	4.4 (12)
Decile 9	3.4 (4)	3.3 (5)	3.3 (9)
Decile 10 (Least deprived)	5.0 (6)	5.2 (8)	5.1 (14)

Data are presented as mean ±standard deviation. Abbreviations: BMI, body mass index; SDS, standard deviation score; BP, blood pressure; IMD, Index Multiple Deprivation. *Black included: African, Caribbean, and other Black. †Asian included: Pakistani, Indian, Bangladeshi, and other Asian. ‡Total number of patients who received a drug for obesity treatment; patients may have received more than one anti-obesity drug during the study period.

Figure 5.10 shows that between 2007 and 2010, more patients received drugs (orlistat, sibutramine, metformin) together with lifestyle intervention than the number of patients who received lifestyle intervention alone. A total of 50 girls received drug treatment together with lifestyle intervention in 2007 and this increased to 65 girls in 2010. Similarly, 23 boys received drugs together with lifestyle intervention for obesity treatment in 2007 and this increased to 43 boys in 2010.

Figure 5.10: Number of patients who received obesity treatment at paediatric weight management clinic



*Drug treatment included: orlistat, sibutramine, or metformin. Lifestyle intervention included exercise advice and healthy eating advice from a dietician. Patients in lifestyle intervention group did not receive any drug for obesity treatment during study period.

Figure 5.11 demonstrates the increase in prescribing of metformin during 2007 and 2010. The number of patients who received metformin increased from 63 in 2007 to 105 in 2010. This increase in metformin prescribing was observed in both girls and boys. It indicates that the majority of patients in this study population may have metabolic syndromes. The number of patients who received orlistat and/or sibutramine was low during this period.

Figure 5.11: Overall Number of patients who received anti-obesity drug treatment by year

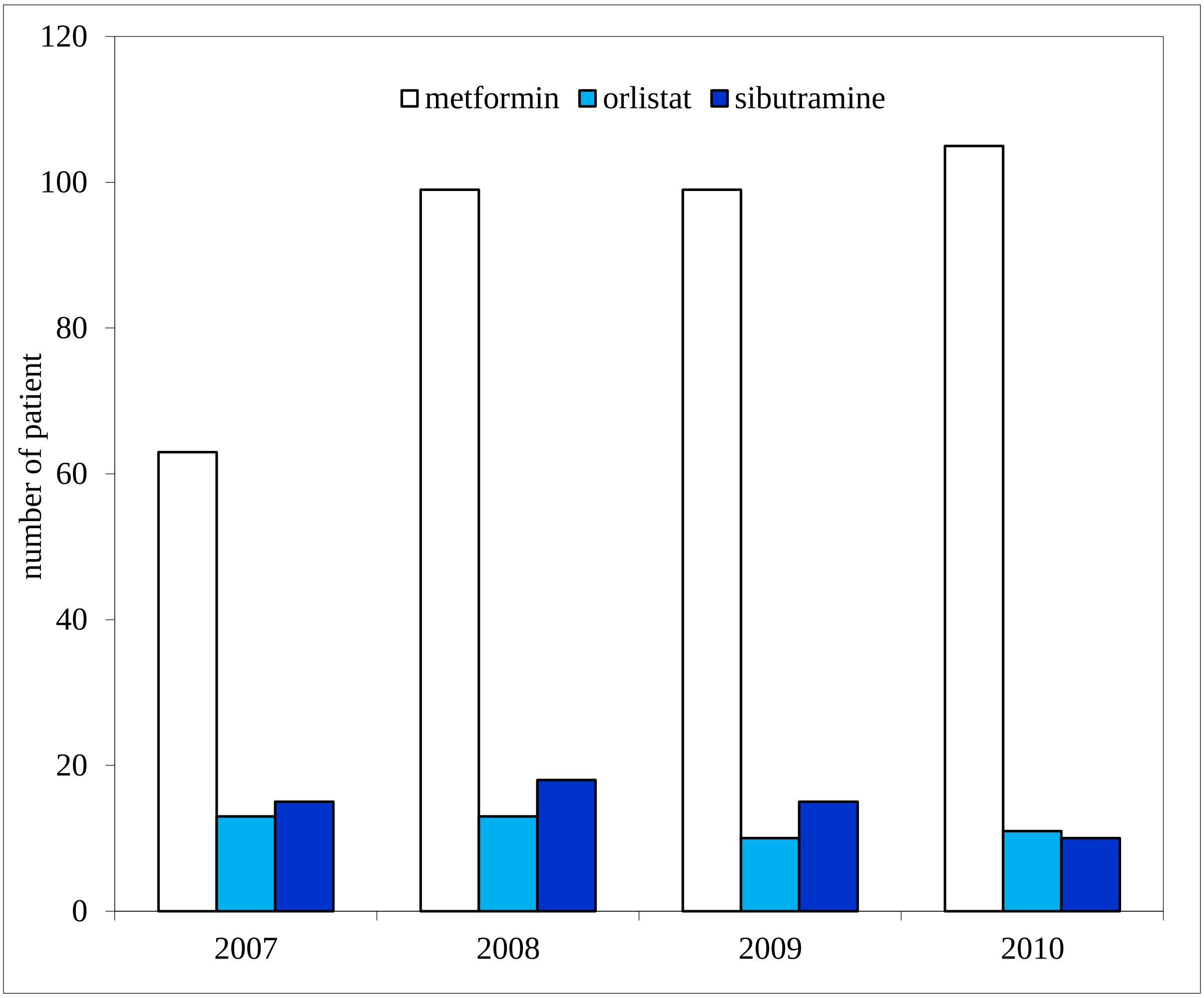
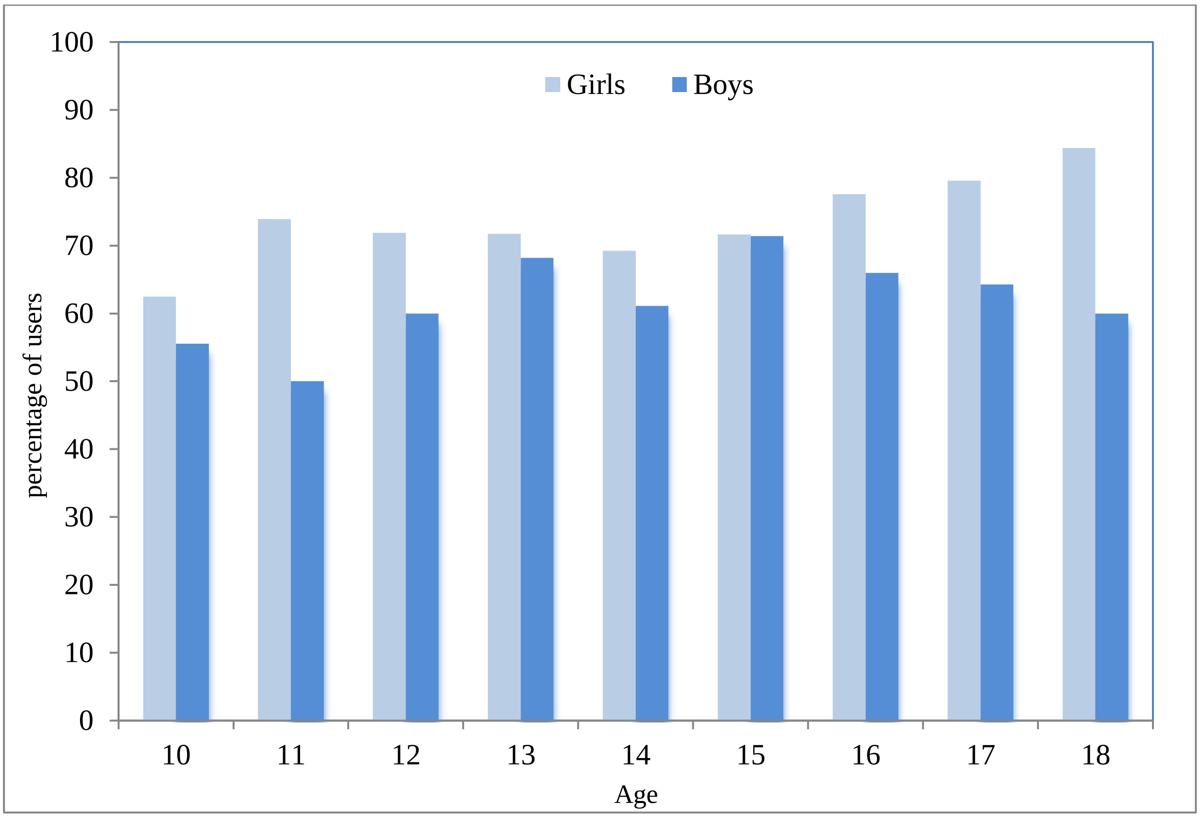


Figure 5.12 shows the percentage of patients who received anti-obesity drugs by sex and age. There was a trend of rising anti-obesity drug prescribing with increasing age particularly in girls. The use of metformin in boys (n=66) was relatively low compared to girls (n=100) during the study period. As a high number of obese girls received metformin in this study population, there is a possibility that these obese girls may also have PCOS and/or diabetes.

Figure 5.12: Percentage of patients who received an anti-obesity drug, by age and sex, 2007-2010



Percentage was calculated by dividing the number of patients who received an anti-obesity drug (orlistat, sibutramine, metformin) for each age and sex by the total number of patients in the study population of the same age and gender multiplied by 100.

5.2.6.Discussion

This is a large cohort study from a regional paediatric weight management clinic investigating drug prescribing patterns for obesity treatment in the UK from 2007-2010. The patients in this study population were mainly girls from a White British background. The study subjects were obese with an overall mean BMI of 36.9 kg/m^2 and a mean BMI SDS of 3.3 at baseline. In addition, boys were observed to have a greater BMI and BMI SDS than girls. From the IMD decile, it was shown that most study subjects were living in the most deprived areas. The association between obesity and deprivation has long been recognised in adults and in children (National Institutes of Health, 1985; Sanjay *et al.*, 2000). A recent national study has demonstrated again the strong association between prevalence of childhood obesity and deprivation in England (Conrad & Capewell, 2012).

Between 2007 and 2010, there were more patients who received drugs (e.g. orlistat, sibutramine, metformin) together with lifestyle intervention (e.g. exercise, diet) for obesity treatment compared to those patients who received lifestyle intervention only and had never received drug treatment for obesity. The release of the NICE guidelines in 2006 may have changed the prescribing behaviour of specialists in the secondary care setting in the UK during this study. However, this explanation should be further examined as we only investigated the drug prescribing practice from one regional specialist clinic so it is not possible to generalise to other clinical centres across the UK.

Metformin was the most frequently prescribed drug for obesity treatment especially in teenage girls at this regional specialist clinic. It is problematic to compare this prescribing pattern with the results in primary care (Section 4.3.4). The data in secondary care were collected from 2007 to 2010 and the study investigating metformin prescribing in primary care was between 2000 and 2010. Further investigation into metformin prescribing in both primary care and secondary care at the same period of time is needed, as this will determine whether metformin use for obesity treatment in young people will continue increase in clinical practice. At present, metformin is only licensed for treatment of type 2 Diabetes Mellitus (DM) in children over 10 years old and also adults. The high number of patients who received metformin may indicate that most patients may have metabolic syndromes such as DM and/or PCOS in girls. Due to the absence of co-morbidity data, it is not known what types of metabolic syndrome coexisted with obesity or how many patients had metabolic syndrome in this study population.

5.2.7.Conclusion

This study provides an insight into the current practice of anti-obesity drug use in young people at the UCLH paediatric weight management clinic. Between 2007 and 2010, more patients received a drug(s) together with lifestyle intervention (exercise and healthy eating advice) for obesity treatment compared to the number of patients who received lifestyle intervention only. This prescribing practice at this specialist care clinic may be attributed to the release of the NICE guideline on weight management in children in 2006. Metformin was the most frequently prescribed drug for obesity treatment and its use increased with age especially in adolescent girls.

5.2.8.Issues leading to additional analyses of the effect of metformin treatment on weight loss

As a high number of patients received metformin for obesity treatment in this study, this raises a question about the effect of metformin treatment on weight loss. As discussed in Chapter 1, due to the limited choice of drugs, several potential drugs have been used for obesity treatment. Of these potential drugs, metformin has been considered the best choice of drug for obesity treatment (Hundal & Inzucchi, 2003). Although metformin has not been licensed for weight reduction in either adults or children to date, it is important to gain a firm understanding of its treatment effect in weight loss in young people, as our study has shown that it is widely used to treat obesity in this population. Therefore, the aim of the next section of this chapter was to investigate the effectiveness of metformin treatment in obese young people in real-life practice. An observational study was conducted to determine the effect of metformin treatment on weight loss in this population. The additional analyses carried out are presented in the next section.

5.3. The effect of metformin treatment on weight reduction in young people

5.3.1. Introduction

As described in 5.1, there have been several RCTs of metformin treatment in obese children and adolescents without diabetes. However, it is not possible to extrapolate findings from RCTs to real-life clinical practice as study participants are highly selected in clinical trials. From the previous analysis in Section 5.2, it was shown that a high number of obese paediatric patients received metformin for obesity treatment. Therefore, an observational study was subsequently conducted to determine the effect of 6 months of treatment with metformin on weight loss in young people.

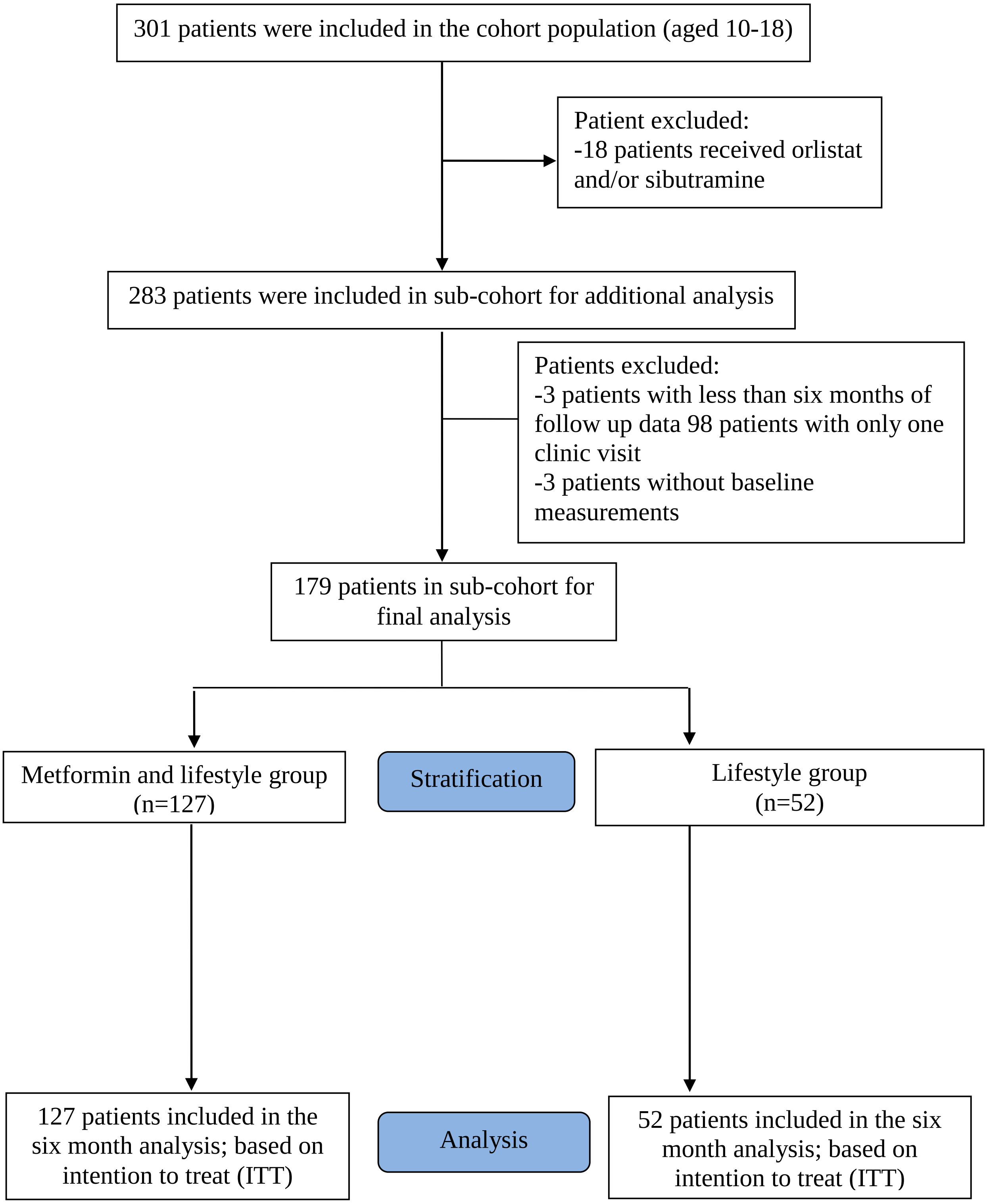
5.3.2. Aim and objectives

The aim of this study was to determine the treatment effect of metformin on weight reduction in young people aged 10-18 years in a real-life practice. The specific objective was to compare BMI, BMI SDS, and weight change for obese patients who received metformin together with lifestyle intervention (exercise advice and healthy eating) with patients who received lifestyle intervention but who did not receive drug treatment, after 6 months of treatment.

5.3.3. Study population

The study population in this additional analysis was derived from the previous cohort study population (n=301). Figure 5.13 shows the number of patients throughout the study. There were 18 patients who received orlistat and/or sibutramine for obesity treatment, these patients were excluded from the final analyses as we did not intend to investigate the treatment effects of these drugs in these analyses. Of the remaining 283 patients, 3 patients with less than 6-months of follow-up, 98 patients who had only one clinic appointment, and 3 patients without baseline measurements were excluded. The remaining 179 patients formed the sub-cohort for the final analyses. These patients were classified into two groups: metformin and lifestyle group (n=127) and the lifestyle only group (n=52).

Figure 5.13: Patient flow: patients with six months follow up during study period (2007-2010)



5.3.4.Statistical Analyses

The demographics and baseline characteristics of the subgroup cohort were described for the metformin and lifestyle intervention group and the lifestyle intervention group. Differences in baseline variables in the two groups were tested by using the independent t-test for continuous variables and the χ^2-test for categorical variables. Data were analysed on an Intention-To-Treat (ITT) approach regardless of compliance (Hollis & Campbell, 1999). Outcomes of BMI, BMI SDS, and weight were post-treatment at 6-month follow-up. These outcomes were tested for normality by using Kolmogorov-Smirnov tests.

Analyses incorporated corrections for missing data on BMI, BMI SDS, and weight, using Multiple Imputation (MI). The MI model was under a "missing at random" (MAR) assumption. The detailed discussion of imputing missing data is presented in the following section. All available baseline and 6 months follow-up measurements were included in the imputation models. The final model was fitted on the basis of multiple imputed datasets using Rubin's rules to combine effect estimates and estimate standard error (Rubin, 1987).

The adjusted mean values on outcomes were adjusted for baseline values using linear regression. The mean differences in BMI, BMI SDS, and weight between groups were analysed using paired t-test at the end of the 6-month follow-up. All analyses used a 2-tailed test with *P* value <0.05 for statistical significance. Stata/MP 11 (StataCorp, College Station, Texas, US) was used for all analyses.

5.3.4.1.Missing data handling

Missing data are a major concern in epidemiological studies, particularly when data need to be collected from individual patients. Inadequately handling missing data in statistical analysis will lead to biased estimates for the outcome of interest. The first step for handling missing data is to understand what and why variables are missing in the dataset. Little and Rubin's framework (2002) has been commonly used to classify the type of missing data. There are three types of missing data mechanism ('missingness' mechanism): missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). The definitions of MCAR, MAR and MNAR are defined below (Little & Rubin, 2002; White *et al*., 2009; Sterne *et al*., 2009):

- Missing completely at random (MCAR): There are no systematic differences between the missing values and the observed values.

- Missing at random (MAR): Any systematic difference between the missing values and the observed values can be explained by differences in observed data.
- Missing not at random (MNAR): Even after the observed data are taken into account, systematic differences remain between missing values and observed values.

The 'missingness' mechanism is only an assumption based on observed data in the database needs to be addressed, and this assumption can then provide guidance on data analysis.

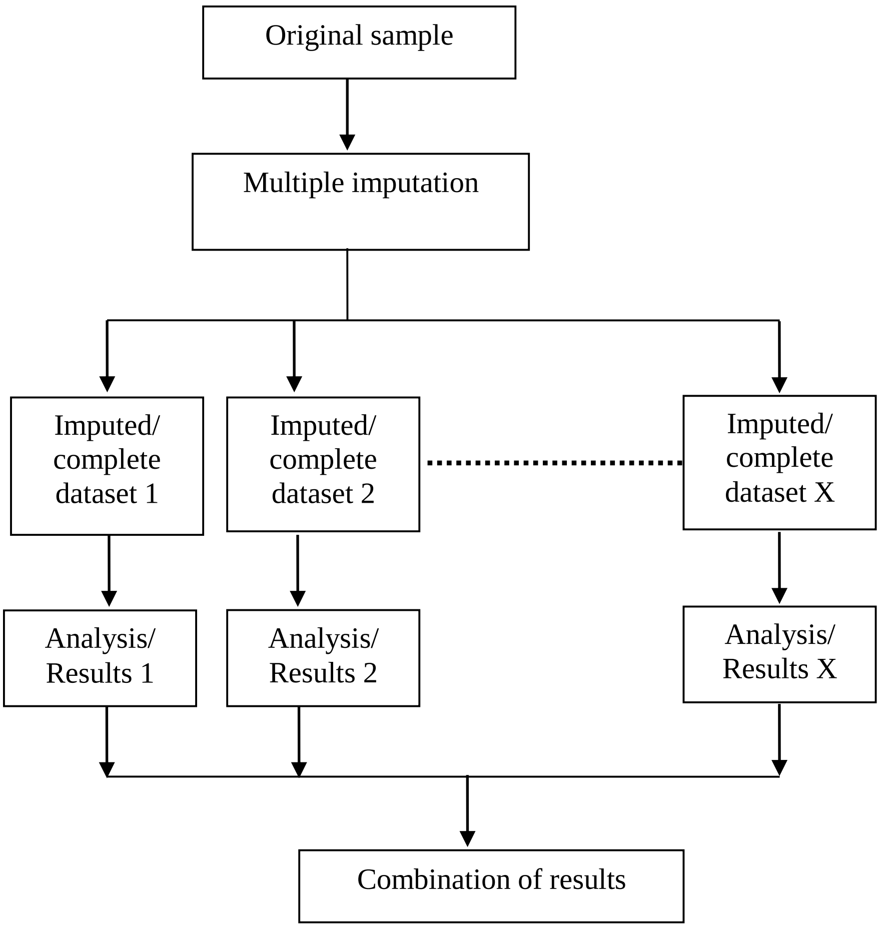
The traditional statistical approach for missing data is to remove individuals with incomplete values (e.g. complete case analysis) by using "listwise deletion" or "casewise deletion" (Fitzmaurice, 2008). The last observation carried forward (LOCF) is another common approach to deal with missing data, especially in obesity studies (Gadbury *et al*., 2003). The LOCF is used to impute the missing value with the individual's last observation. It is based on the assumptions that the missing value has not changed from the previous measurement (Wood *et al*., 2004). All these traditional approaches may lead to a reduction of precision estimates in statistical analysis.

In recent years, several advanced statistical techniques such as maximum likelihood-Expectation–Maximization (EM) algorithm, single random imputation, and multiple imputation (MI) have become increasingly popular in medical research due to software development (Mackinnon, 2010). In general, these statistical techniques replace missing data with estimates from observed values which overcome the limitations of the traditional approaches. Each of these techniques has their advantages and disadvantages. However, as detailed information for individual statistical techniques is beyond the scope of this thesis, the following discussion is restricted to multiple imputations which was used in this study.

MI is used to impute (or fill in) missing values by using a regression model based on the individual's data (Wood *et al*., 2004). The advantage of using MI is that it takes all variances into account to generate more reliable estimates compared to the traditional methods (Wood *et al*., 2004; Sterne *et al*., 2009). Figure 5.14 shows the process of MI. The

MI works by imputing the missing values, with predications from observed data, multiple times. This step will create a set of complete datasets with no missing values. The analysis is then run individually on each dataset and the final results are combined across the entire data set using Rubin's combination rule (Rubin, 1987).

Figure 5.14: Multiple imputation process



In this study, as the dataset contained missing values, it warranted comprehensive data cleaning prior to final analysis. The data cleaning process for this study was broken down into the following steps:

Step 1: To describe missing variables and assess the 'missingness' mechanism.
There were 1152 records for the variables (BMI, BMI SDS, blood pressure) captured in this sub-cohort population (n=283). The percentage of missing values for each variable ranged from 15.9% to 48.3% (Table 5.4). For blood pressure measurements, values were not recorded for approximately half of the patients in the dataset.

Table 5.4: Percentage of missing records in study cohort

Variable name	Description	No. of missing records	% missing
Weight	Weight measured at each clinic visit	183	15.9
Height	Height measured at each clinic visit	183	15.9
BMI	Calculated from weight and height	183	15.9
BMI SDS	Calculated from ImsGrowth programme	183	15.9
Systolic blood pressure	Blood pressure measured at each clinic visit	556	48.3
Diastolic blood pressure	Blood pressure measured at each clinic visit	556	48.3

Abbreviations: BMI, body mass index; SDS, standard deviation score.

The 'missingness' mechanisms of BMI, BMI SDS, and weight were examined between patients without missing records and patients with missing records. As blood pressure was not the main outcome of interest in this study, those missing blood pressure records were not included in the multiple imputations. As the 'Missing At Random' (MAR) is defined as *'any systematic difference between the missing values and the observed values can be explained by difference in observed data'* (Sterne et al., 2009). The missing pattern in our study population appears to be MAR as patients without missing records have lower BMI, BMI SDS, and weight compared to patients with missing values in both sexes (Table 5.5). This may be due to extremely obese patients being more reluctant to be measured than patients with a lower BMI.

Table 5.5: Description of the 'missingness' mechanisms in study cohort

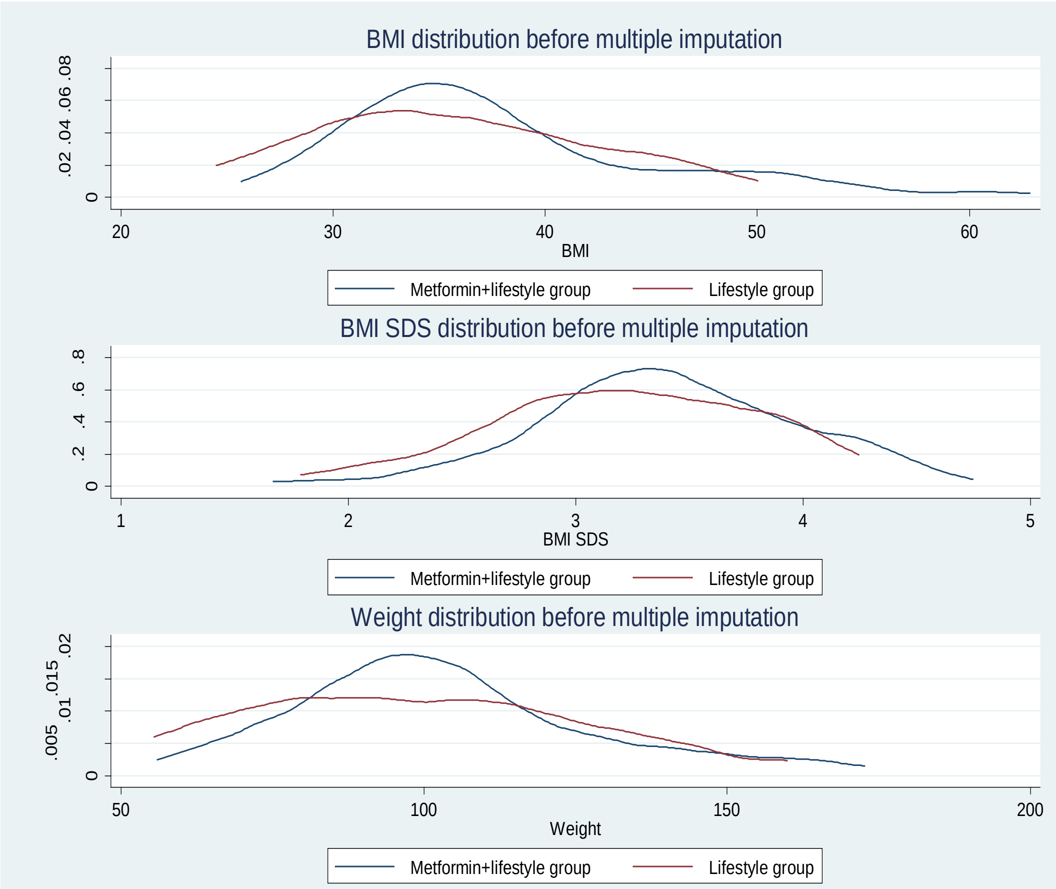
Patients with missing records		Patient without missing records	
	Mean (s.e.)		Mean (s.e.)
Boys		Boys	
BMI	39.87±0.66	BMI	37.63±0.59
BMI SDS	3.47±0.04	BMI SDS	3.33±0.04
Weight	120.88±2.40	Weight	106.11±1.99
Girls		Girls	
BMI	37.12±0.59	BMI	35.67±0.38
BMI SDS	3.18±0.07	BMI SDS	3.19±0.04
Weight	97.09±1.45	Weight	94.62±1.22

Abbreviations: BMI, body mass index; SDS, standard deviation score. s.e., standard error.

The best approach for dealing with the MAR pattern of missing values is the Multiple Imputation by Chained Equation (MICE) procedure (Schafer & Graham, 2002). The MICE procedure is also known as the "fully conditional specification" or "sequential regression multiple imputation" (Azur *et al*., 2011). This is a flexible approach as it can handle variables of varying types such as continuous or binary (Raghunathan *et al*., 2001; Azur *et al*., 2011). The MICE approach is particularly useful for handling missing data in a large dataset as missing data may occur in different types of variables. Therefore, the MICE procedure has become a popular approach in recent years, for handling multiple imputations (Royston and White 2011). The MICE package is implemented in Stata software. In this study, the MICE procedure was used for imputing missing values on BMI, BMI SDS, and weight.

Step 2: To examine the normality of the data distribution between the metformin-treated group and the non-pharmacologically treated group, before carrying out the MI procedure. The two-sample Kolmogorov-Smirnov test was used to examine whether there were differences in the distributions of BMI, BMI SDS, and weight between the two groups. Figure 5.15 shows that there were no significant differences in the distribution of BMI, BMI SDS, and weight values, between the two groups.

Figure 5.15: Distribution of recorded BMI, BMI SDS, and weight between the metformin and lifestyle group and the lifestyle group before multiple imputation



Two-sample Kolmogorov-Smirnov test for equality of distribution: BMI

Smaller group	D	P-value	Corrected
1:	0.0318	0.938	
2:	-0.1636	0.186	
Combined K-S:	0.1636	0.369	**0.297**

Two-sample Kolmogorov-Smirnov test for equality of distribution: BMI SDS

Smaller group	D	P-value	Corrected
1:	0.0091	0.995	
2:	-0.1955	0.091	
Combined K-S:	0.1955	0.181	**0.134**

Two-sample Kolmogorov-Smirnov test for equality of distribution: Weight

Smaller group	D	P-value	Corrected
1:	0.0864	0.626	
2:	-0.1591	0.204	
Combined K-S:	0.1591	0.404	**0.330**

Step 3: To impute missing values for BMI, BMI SDS, and weight using the MICE approach. The Stata command for the MICE approach is '**ice**'. In the imputed dataset, it includes incomplete variables (e.g. BMI, BMI SDS, weight, height) as well as complete variables (e.g. sex, age, treatment condition). In general, 5 to 10 imputed datasets are considered to be enough to achieve high efficiency (Rubin, 1987). In recent years, it has been recommended that more imputation such as 20 imputations (*m*=20) or 100 imputations (*m*=100), will be beneficial (Graham *et al*, 2007). However, more imputations will increase the computational effort. In this study, twenty copies of imputed datasets (*m*=20) were created. The imputation procedure in the Stata programme is given below:

```
. ice gender met weight1 weight2 bmi2 sds_bmi2, gen(m_)
saving("mi_20", replace) m(20) seed(29390)

   #missing |
     values |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |        112       87.50       87.50
          3 |         16       12.50      100.00
------------+-----------------------------------
      Total |        128      100.00

   Variable | Command | Prediction equation
------------+---------+-------------------------------------------
------------
     gender |         | [No missing data in estimation sample]
        met |         | [No missing data in estimation sample]
    weight1 |         | [No missing data in estimation sample]
    weight2 | regress | gender met weight1 bmi2 sds_bmi2
       bmi2 | regress | gender met weight1 weight2 sds_bmi2
   sds_bmi2 | regress | gender met weight1 weight2 bmi2
------------------------------------------------------------------
Imputing
..........1..........2..........3..........4..........5..........6
......7..........8..........9..........10..........11..........12.
.........13..........14..........15..........16..........17.......
...18..........19.....> .....20
file mi_20.dta saved
```

Step 4: To examine the imputed data and observed data to ensure that the imputed data are reasonable. The graphs are presented for the imputed data and the observed data for BMI, BMIS SDS, and weight (see Appendix 13). The Two-sample Kolmogorov-Smirnov test was used to examine whether the imputed data and the observed data were normally distributed. The summary statistics of mean, median and inter-quartile range (IQR) are presented for BMI, BMI SDS, and weight in Table 5.6. This shows that the imputed data were very similar to those from observed data. The imputed data in the final dataset appear reasonable for final analysis.

Step 5: To analyse the multiple imputed data. After the imputations were created and the examined imputed data were reasonable, the 20 imputed datasets were used for the final analyses. As mentioned earlier, the analysis was run individually within each complete dataset then the results were combined using Rubin's rules.

Table 5.6: Summary statistics for BMI, BMI SDS and weight, from recorded data and imputed data at 6 month follow-up period

	Recorded data at 6 months			Imputed data at 6 months		
Metformin and lifestyle group	Mean (s.e.)	Median	IQR (IQR range)	Mean (s.e.)	Median	IQR (IQR range)
BMI	37.77±0.48	36.06	7.56 (32.92-40.48)	37.77±0.46	36.21	7.69 (32.92-40.61)
BMI SDS	3.41±0.04	3.38	0.66 (3.10-3.76)	3.41±0.03	3.38	0.67 (3.09-3.76)
Weight	102.52±1.63	99.20	29.4 (86.30-115.70)	102.51±1.58	99.27	29.7 (86.30-115.98)
Lifestyle group						
BMI	35.67±0.72	34.82	9.51 (31.39-40.90)	35.69±0.69	34.87	9.59 (31.34-40.93)
BMI SDS	3.19±0.08	3.22	0.80 (2.90-3.70)	3.19±0.08	3.21	0.80 (2.89-3.69)
Weight	98.62±2.83	98.00	43.90 (77.10-121.0)	98.56±2.73	97.88	40.71 (78.03-118.74)

Abbreviation: BMI, body mass index; SDS, standard deviation score; IQR, inter-quartile range; s.e, standard error. IQR is the difference between first quartile (Q1) and third quartile (Q3).IQR is calculated as Q3minus Q1.

5.3.5.Results

5.3.5.1.Baseline characteristics of sub-cohort subjects

Table 5.7 shows the baseline characteristics of the sub-cohort (n=179) and the two treatment groups. There were more girls than boys in both groups. Over half of the patients were White British in the metformin and lifestyle group (63.8%) and the lifestyle group (63.5%). Mean BMI SDS was 3.4 in metformin group which indicates that these patients were extremely obese, and it was significantly higher than that of the lifestyle group. There were no other significant differences between the groups for baseline demographic, weight, height, BMI, or blood pressure (systolic and diastolic).

In this sub-cohort study, the IMD distribution showed that more patients were living in the more deprived areas (decile 1=14.5%; decile 2=24%) than in the less deprived deciles (decile 9 =2.2%; decile 10=3.9%). This was similar in both groups and there was no significant difference between the groups (p=0.51).

Table 5.7: Comparison of baseline characteristics of patients (aged 10-18 years) between treatment groups

	Sub-cohort (n=179)	Metformin and lifestyle (n=127)	Lifestyle (n=52)	Statistic	*P*-value
Age (year)	13.9 (2.11)	13.9 (2.12)	13.8 (2.09)	*t*=0.2	0.86
Gender % (n)				χ^2=1.0	0.31
Girls	55.9 (100)	58.3 (74)	50.0 (26)		
Boys	44.1 (79)	41.7 (53)	50.0 (26)		
Ethnicity % (n)				χ^2=7.5	0.18
British White	63.7 (114)	63.8 (81)	63.5 (33)		
Black	11.2 (20)	10.2 (13)	13.5 (7)		
Asian	7.3 (13)	8.7 (11)	3.8 (2)		
Mixed	7.3 (13)	9.4 (12)	1.9 (1)		
Other ethnic group	2.2 (4)	1.6 (2)	3.8 (2)		
Not stated	8.4 (15)	6.3 (8)	13.5 (7)		
Weight (kg) *(n=154)*	100.6 (26.0)	101.6 (25.2)	97.9 (28.01)	*t*=0.85	0.40
Height (cm) *(n=154)*	163.9 (11.7)	163.6 (11.6)	164.8 (12.0)	*t*=-0.61	0.54
BMI (kg/m^2) *(n=154)*	37.0 (7.3)	37.6 (7.2)	35.5 (7.4)	*t*=1.76	0.08
BMI SDS *(n=154)*	3.3 (0.7)	3.4 (0.5)	3.2 (0.9)	*t*=2.27	0.02*
BP *(n=128)*					
Systolic BP (mmHg)	127.7 (16.6)	127.9 (18.2)	127.1 (11.6)	*t*=0.23	0.81
Diastolic BP (mmHg)	72.7 (9.7)	73.8 (9.9)	70.2 (8.7)	*t*=1.89	0.06
IMD 2007 decile % (n) *(n=163)*				χ^2=8.3	0.51
Decile 1 (Most deprived)	14.5 (26)	14.2 (18)	15.4 (8)		
Decile 2	24.0 (43)	23.6 (30)	25.0 (13)		
Decile 3	15.1 (27)	14.9 (19)	15.4 (8)		
Decile 4	9.5 (17)	7.9 (10)	13.5 (7)		
Decile 5	6.1 (11)	5.5 (7)	7.7 (4)		
Decile 6	5.6 (10)	5.5 (7)	5.8 (3)		
Decile 7	6.1 (11)	7.9 (10)	1.9 (1)		
Decile 8	3.9 (7)	5.5 (7)	0.0 (0)		
Decile 9	2.2 (4)	3.1 (4)	0.0 (0)		
Decile 10 (Least deprived)	3.9 (7)	3.9 (5)	3.8 (2)		

Abbreviation: BMI, body mass index; SDS, standard deviation score; BP, blood pressure; IMD, Index Multiple Deprivation. Patients in each group all received lifestyle intervention (e.g. dietician for healthy eating advice and medical advice).The figures are presented as means±s.d (standard deviation), or number % (n) percentage of total. Significant differences of values are indicated as $^*P$<0.05.

5.3.5.2.Within-group change

The effects of metformin treatment together with lifestyle intervention and those of lifestyle intervention alone are shown in Table 5.8. In the metformin and lifestyle group, both boys and girls experienced a significant reduction in BMI SDS at the end of the 6 month period of treatment. However, whereas the girls had a significant reduction in BMI with metformin treatment and lifestyle intervention ($p=0.001$) the boys ($p=0.38$) did not. The patients' body weights were slightly increased in both the metformin and lifestyle intervention group and the lifestyle group. After adjustment for baseline weight, there was significant increase in weight for both boys and girls in the metformin and lifestyle group. In the lifestyle group, there were no significant changes in either BMI or in weight for both boys and girls. However there was a significant reduction in BMI SDS for boys ($p<0.0001$) but a significant increase of BMI SDS for girls ($p<0.0001$) in the lifestyle group.

Table 5.8: Within-group changes at 6 months of treatment

	Baseline mean	Adjusted Mean	Mean change	P value
Metformin and lifestyle group				
All (n=127)				
BMI (kg/m^2)	37.65 ± 0.45	37.55 ± 0.26	-0.10 (0.05)	0.03^{*}
BMI SDS	3.42 ± 0.03	3.38 ± 0.02	-0.04 (0.03)	$<0.0001^{**}$
Weight (kg)	101.64 ± 1.58	102.79 ± 0.61	+1.15 (0.15)	$<0.0001^{**}$
Height (cm)	163.64 ± 0.72	164.76 ± 1.04	+1.12 (1.26)	0.37
Boys (n=53)				
BMI (kg/m^2)	38.17 ± 0.74	38.29±0.66	+0.12 (0.14)	0.38
BMI SDS	3.45 ± 0.05	3.42 ± 0.07	-0.03 (0.01)	0.01^{*}
Weight (kg)	108.24 ± 2.66	109.76 ± 1.47	+1.52 (0.42)	0.0004^{**}
Height (cm)	167.75 ± 1.28	169.5±1.79	+1.75 (2.19)	0.42
Girls (n=74)				
BMI (kg/m^2)	37.28 ± 0.57	36.99 ± 0.43	-0.29 (0.08)	0.001^{**}
BMI SDS	3.40 ± 0.05	3.33 ± 0.04	-0.07 (0.01)	$<0.0001^{**}$
Weight (kg)	96.91 ± 1.84	98.16 ± 0.99	+1.25 (0.24)	$<0.0001^{**}$
Height (cm)	160.70 ± 0.76	161.33 ± 1.08	+0.63 (1.32)	0.63
Lifestyle group				
All (n=52)				
BMI (kg/m^2)	35.55 ± 0.72	35.52 ± 0.72	-0.03 (0.14)	0.83
BMI SDS	3.17 ± 0.09	3.22 ± 0.05	+0.05 (0.01)	0.001^{**}
Weight (kg)	97.98 ± 2.73	98.61 ± 1.49	+0.63 (0.43)	0.15
Height (cm)	164.82 ± 1.17	165.89 ± 1.62	+1.07(1.99)	0.59
Boys (n=26)				
BMI (kg/m^2)	36.78 ± 0.88	36.90 ± 0.89	+0.12 (0.25)	0.63
BMI SDS	3.36±0.08	3.27 ± 0.07	-0.09 (0.02)	$<0.0001^{**}$
Weight (kg)	104.22 ± 3.74	103.45 ± 2.14	-0.77 (0.84)	0.36
Height (cm)	167.22 ± 1.82	168.49 ± 2.55	+1.27 (3.13)	0.68
Girls (n=26)				
BMI (kg/m^2)	34.30 ± 1.12	34.47 ± 1.42	+0.17 (0.35)	0.63
BMI SDS	2.97 ± 0.16	3.13 ± 0.08	+0.16 (0.03)	$<0.0001^{**}$
Weight (kg)	91.74 ± 3.82	92.01 ± 2.58	+0.27 (0.90)	0.76
Height (cm)	162.43 ± 1.42	163.28 ± 1.92	+0.85 (2.38)	0.72

Abbreviation: BMI, body mass index; SDS, standard deviation score. Figures represent means± standard error. Patients in each group all received lifestyle intervention (e.g. dietician for healthy eating advice and medical advice). The 6-month follow up data were calculated based on the intention-to-treat (ITT) with imputed datasets. Adjusted mean was adjusted from baseline value using linear regression for multiple imputation data. Significant differences of values are indicated as $^{*}P<0.05$ or $^{**}P<0.01$.

5.3.5.3.Between-group changes

Table 5.9 shows the between-group changes. Overall, there were no significant between-group differences for BMI, BMI SDS, weight, and height. The height was increased in both the metformin and lifestyle group and also in the lifestyle group, as well as in both sexes, but this increase was not significantly different between the two groups. However, there was a significant effect of metformin treatment with lifestyle intervention on BMI SDS in girls compared to only lifestyle intervention [difference between metformin and lifestyle group and lifestyle group: -0.23; 95% CI -0.28 to -0.18, p<0.0001]. There was a significant increase of BMI by 0.12 mg/m^2 and of weight by 1.52 mg/m^2 in boys after 6 months of metformin treatment.

Table 5.9: Between-group changes at 6 months treatment

	Metformin and lifestyle (n=127)	Lifestyle (n=52)	Mean difference (95% CI)	*P* value*
All				
BMI (kg/m^2)	-0.10 (0.05)	-0.03 (0.14)	-0.07 (-0.38 to 0.16)	0.55
BMI SDS	-0.04 (0.03)	+0.05 (0.01)	-0.09 (-0.18 to 0.003)	0.06
Weight (kg)	+1.15 (0.15)	+0.63 (0.43)	+0.52 (-0.19 to 1.23)	0.15
Height (cm)	+1.12 (1.26)	+1.07 (1.99)	+0.05 (-4.57 to 4.67)	0.98
	Metformin and lifestyle (n=53)	Lifestyle (n=26)	Mean difference (95% CI)	*P* value
Boys				
BMI (kg/m^2)	+0.12 (0.14)	+0.12 (0.25)	0.0 (-0.53 to 0.53)	1.0
BMI SDS	-0.03 (0.01)	-0.09 (0.02)	+0.06 (0.02 to 0.09)	0.003**
Weight (kg)	+1.52 (0.42)	-0.77 (0.84)	+2.29 (1.07 to 3.51)	0.0004**
Height (cm)	+1.75 (2.19)	+1.27 (3.13)	+0.48 (-7.12 to 8.08)	0.90
	Metformin and lifestyle (n=74)	Lifestyle (n=26)	Mean difference (95% CI)	*P* value
Girls				
BMI (kg/m^2)	-0.29 (0.08)	+0.17 (0.35)	-0.46 (-0.95 to 0.03)	0.06
BMI SDS	-0.07 (0.01)	+0.16 (0.03)	-0.23 (-0.28 to -0.18)	<0.0001**
Weight (kg)	+1.25 (0.24)	+0.27 (0.90)	+0.98 (-0.34 to 2.30)	0.14
Height (cm)	+0.63 (1.32)	+0.85 (2.38)	-0.22 (-5.44 to 5.00)	0.93

Abbreviations: BMI, body mass index; SDS, standard deviation score; CI, confidence interval. The figures are presented as means and s.e (standard error). The 6-month follow up data were calculated based on the intention-to-treat (ITT) with imputed datasets. Mean difference: metformin and lifestyle group minus lifestyle group. Significant differences of values are indicated as $^{*}P<0.05$ or $^{**}P<0.01$.

5.3.6. Discussion

This cohort study sought to determine the effect of metformin treatment combined with lifestyle intervention on weight loss in obese young people treated in the NHS. In this non-randomised controlled clinic-based sample, we found that metformin treatment together with standard care lifestyle advice resulted in a statistically significant decrease of BMI SDS in both boys and girls and a reduction of BMI in girls compared to baseline. When compared with standard care alone, the metformin group had a small but significant increase in BMI and BMI SDS loss at 6 months in girls, but a very slightly statistically significant increase in BMI SDS amongst boys.

Strength and limitations

This is the first known observational study to investigate metformin treatment in obese young people at a regional specialist clinic in the UK or elsewhere. However, this study is subject to several methodological limitations. Firstly, as the data were collected from one paediatric weight management clinic, our findings cannot necessarily be generalised. However, given that the clinic used is one of the largest in the UK, findings are likely to be similar in other specialist paediatric weight management services seeing young people of comparable BMI. Secondly, our estimated metformin treatment effect may be biased by the differences in baseline risk for other underlying factors and/or other treatment interventions. This limitation is due to the absence of information on co-morbidities, co-prescribing medication, and other interventions (e.g. psychological intervention) that patients may also have received for obesity treatment. An observational study is widely used to investigate drug treatment effects in routine clinical practice, as this type of study design allows a broader population of patients to be included which may sometimes be excluded from RCTs (e.g. young children, patients with severe co-morbidities) (Klungel *et al*., 2004). The main concern in assessing the effect of drug treatment in observational studies is confounding factors. It has been suggested that sufficient baseline information should be collected to analyse confounding by pre-existing differences, when comparing treated and untreated groups in an observational study (Jepsen *et al*., 2004; Stürmer *et al*., 2007). A variety of individual or group therapies (e.g. psychological intervention, behavioural therapies) have been recommended for weight management (NICE 2006). Young people are also likely to be undertaking a range of self-initiated actions such as self-directed diets, exercise programmes or involvement in commercial weight management programmes. However, we do not have information on other weight management activities young people in the clinical cohort had self-initiated. Thirdly, the data on waist circumference were not available from the records as this is not measured routinely in the clinic. Thus, the impact of metformin on change in visceral adiposity could not be assessed. The study did not have access to adequate data on cardiometabolic risk for this study cohort. The data obtained in the study were not of sufficient quality to be used in these analyses due to very high levels of missing data. Therefore, we were unable to investigate whether metformin improved cardiometabolic risk in these obese young people, nor whether those with insulin insensitivity responded better to metformin than those with normal insulin sensitivity.

A further limitation is missing data for the BMI outcomes. All patients should have had their weight and height recorded before each consultation. However, there was a relatively high proportion of missing measurements for weight and height in the current database. There are two possible reasons for missing measurements in the present study: (i) clinical procedures; (ii) patient refusal. Weight and height are normally measured by nurses at the clinic, and these measurements may sometimes not be recorded in patient's medical notes. It was observed that patients with higher BMI have more missing measurements compared to patients with lower BMI. This suggests that some patients may refuse to be weighted at clinic, resulting in missing measurements in their medical notes. Finally, the study did not assess adherence or adverse effects as these data were not routinely collected in a usable form. Metformin dose in the present study was not examined. The data in the study were collected from a paediatric management clinic and we do not know the reasons patients changed metformin dosage during the 4-year study period. Data from real-life clinic practice are different from RCT data, as clinicians are required to follow a standardised protocol to adjust dosage use.

Comparison with previous studies

No comparable data on metformin treatment in routine NHS practice has been published in the UK. The only comparable data on metformin treatment effect come from RCTs, although patients in the RCT are usually highly selected and generally more motivated in terms of adherence. The reduction in BMI SDS of -0.23SD identified in girls at 6 months, equivalent to 0.46kg/m^2 reduction in BMI, is less than the 1.4kg/m^2 estimate of BMI reduction reported by the systematic review by Park et al (2009). It is however similar to the effect size reported in the only UK RCT, which reported that metformin resulted in a -0.1SD (-0.18, -0.02) reduction in BMI SDS compared with placebo at 6 months (Kendall *et al*., 2013). We found an effect for metformin in girls but not boys in our study. This is consistent with a US study by Love-Osborne and colleagues (2008). They reported a statistically significant reduction of BMI by 0.40 kg/m^2 in girls with metformin (n=33) treatment compared with 1.04 kg/m^2 in placebo group (n=9). This treatment effect was not seen in boys with metformin treatment. The authors gave several explanations: 1) this may represent true sex differences in the action of metformin; 2) the underlying differences in mechanism or degree of insulin resistance; 3) girls were more likely to report a decrease in portion size than boys when they were taking metformin or placebo (Love-Osborne et al. 2008). However, the reasons for a sex difference in metformin response remain unclear to date. Further investigation is warranted on the metformin treatment effect on the gender difference in this population.

5.3.7. Conclusion

The data from this study suggests that metformin can be effective in reducing BMI in obese adolescent females over 6 months in routine clinical practice, although the benefits are less than those seen in RCTs. There was no evidence of benefit in obese young men. The effect size seen in clinical practice is small and of borderline clinical significance. However, any benefits no matter how small can be important in the difficult field of weight management, as they may presage gradual weight loss over time. Metformin is currently only licensed for the treatment of type 2 diabetes in adolescents and not specifically indicated for the treatment of obesity. The current evidence on metformin use for weight loss is based on small and short-term RCTs in young people. There is a clear need for longer larger scale RCTs in obese children and adolescents to meaningfully assess the place of metformin and identify subgroups most likely to benefit.

Chapter 6 Anti-obesity drug prescribing to young people in primary care and secondary care: a national questionnaire survey

6.1.Introduction

Clinical guidelines for prevention and treatment of obesity (Scottish Intercollegiate Guidelines Network, NICE) recommend a multicomponent approach for obesity treatment in obese young people in primary care. The recommendations for treating obese and overweight children in primary care include: 1) to measure height and weight and assess co-morbidities; 2) discuss weight issues and give advice to parents and/or guardian or carers; 3) treatment approaches include: lifestyle intervention, behavioural intervention, physical activity, and dietary advice; 4) pharmacological intervention should only be considered after above-mentioned approaches have been started and evaluated; 4) referral to appropriate specialist in secondary care. Pharmacological intervention used in childhood obesity management is described in Chapter 1, section 5. Pharmacological intervention is recommended for childhood obesity in the NICE guidelines for certain circumstances. Since the withdrawal of sibutramine, the more recent NICE guidelines suggest that orlistat should be considered a useful adjunct to lifestyle intervention in adolescents ≥12 years old with physical co-morbidities and that use in <12 years should be reserved for those with life-threatening co-morbidities (NICE 2006). The recently revised NICE recommendation on pharmacological intervention for obesity treatment in young people is presented in Table 6.1.

Sometimes lifestyle intervention change alone fails to achieve weight loss in young people, so the combination of lifestyle intervention and medication should be considered (August et al., 2008). However, lifestyle change remains the most appropriate intervention for childhood obesity management, but anti-obesity drugs together with lifestyle intervention may offer additional benefits for weight loss. A Cochrane review included 64 RCTs (5,230 study participants) to investigate the efficacy of lifestyle intervention, anti-obesity drug and surgical interventions for childhood obesity treatment (Oude *et al.,* 2009). The results of the Cochrane review support the consideration of pharmacological therapy as adjunct to lifestyle interventions in obese adolescents; however, the authors state that this approach needs to be carefully weighed against the potential adverse effects of drug treatment.

Table 6.1: Revised NICE guideline* recommendations for pharmacological intervention in children

General: indications and initiation
1. Pharmacological treatment should be considered only after dietary, exercise and behavioural approaches have been started and evaluated
2. Drug treatment is not generally recommended for children younger than 12 years
3. If children younger than 12 years, drug treatment may be used only in exceptional circumstances, if severe life-threatening comorbidities (such as sleep apnoea or raised intracranial pressure) are present. Prescribing should be started and monitored only in specialist paediatric settings.
4. In children are aged 12 years and older, treatment with orlistat is recommended only if physical comorbidities (such as orthopaedic problems or sleep apnoea) or severe psychological comorbidities are present. Treatment should be started in a specialist paediatric setting, by a multidisciplinary team with experience of prescribing in this age group.
5. Orlistat should be prescribed for obesity in children only by a multidisciplinary team with expertise in: • Drug monitoring • Psychological support • Behavioural interventions • Interventions to increase physical activity • Interventions to improve diet
6. Orlistat should be prescribed only if the prescriber is willing to submit data to the proposed national registry on the use of these drugs in young people.
7. After drug treatment started by specialist care, it may be continued in primary care if local circumstances and/or licensing allow.
Continued prescribing and withdrawal
1. Pharmacological treatment may be used to maintain weight loss, rather than for continued weight loss.
2. If there is concern about the adequacy of micronutrient intake, a supplement providing the reference nutrient intake for all vitamins and minerals should be considered, particularly for vulnerable groups such as young people (who need vitamins and minerals for growth and development).
3. Where drug treatment is being withdrawn, support should be offered on maintaining weight loss, as their self-esteem and belief in their ability to make changes may be low if target weight was not achieved.
4. If orlistat is prescribed for children, a 6-12-month trial is recommended, with regular reviews to assess effectiveness, adverse effects and adherence.

*Sibutramine was previously included in the NICE guideline. After the withdrawal of sibutramine in UK in 2010, the current NICE guidelines only recommend orlistat for obesity treatment in young people.

Childhood obesity is one of the highest health priorities in the UK. It is routine practice for general practitioners (GPs) to continue obesity management after recommendation from specialists in secondary care in the UK. Primary care has the potential to play a pivotal role in obesity management in the UK primary care setting (Epstein & Ogden 2005). In 2002, the National Service Frameworks issued by the Department of Health stated that primary care should *"use every opportunity to promote healthy lifestyle, and should provide advice on diet, weight reduction, and exercise"* (Department of Health 2002). Doctors regularly miss opportunities to discuss weight with their patients but there is good evidence that physician acknowledgement can trigger lifestyle changes (Post *et al.,* 2011). In 2006, measurement of obesity using body mass index (BMI) for adults but not for children was included in the National Quality and Outcome Framework (QOF) scheme, as a pay-for-performance scheme offering financial rewards to GPs for achieving targets in managing and measuring chronic disease (Roland 2004). The Department of Health published a care pathway for the assessment and management of overweight and obese young people and children in primary care, in order to assist practitioners tackling obesity in young people (Department of Health, 2006). The NICE guidelines on obesity management in adults and young people were first published in 2006 and had a strong focus on obesity management in primary care advocating dietary advice and increased physical activity as first line management. However, lifestyle interventions need to be intensive to achieve weight reduction and sustained to continue to be effective. This can pose particular challenges for managing obesity in children and adolescents and GPs who need to interact with the family as a whole (Matson & Fallon, 2012; King *et al.,* 2007). In recent years, a number of studies have been conducted to examine practitioners' views in managing childhood obesity in primary care (Jelalian *et al.,* 2003; Goldman *et al.,* 2004; Gerner *et al.,* 2006; Spurrier *et al.,* 2006; Walker *et al.,* 2007; King *et al.,* 2007; Turner *et al.,* 2009; Gage *et al.,* 2010). The majority of these studies were carried out in other countries (e.g. US, Australia); there is little published research on childhood obesity management in UK primary care (Walker *et al.,* 2007; Turner *et al.,* 2009; Gage *et al.,* 2010).

In the UK, an interview study of 12 GPs and 6 nurses working in a GP practice, contracted to Rotherham Primary Care Trust (PCT), has shown that GPs and practice nurses felt childhood obesity was sometimes a problem, which was difficult to address (Walker *et al.,* 2007). The authors expressed the difficulties in treating childhood obesity: they do not want to upset the child and parents by bringing attention to the child's weight and concerns about breakdown in family relationships if the problem of a child's weight is mentioned. Another qualitative UK-based study was conducted after the publication of the childhood obesity care pathway and the NICE guidelines. In this study which was carried out in Bristol 30 practitioners (12 GPs, 10 practice nurses, 4 school nurses, and 4 health visitors) from 7 general practices were interviewed (Turner *et al.*, 2009). All practitioners felt that they were concerned about the current childhood obesity epidemic, but none had seen the Department of Health's obesity care pathway for young people. Only 2 GPs and 1 practice nurse had looked at the NICE obesity guideline. A questionnaire survey of GPs and parents was conducted to explore their opinions on childhood obesity management in southern England. There was a clear difference between GPs and parents' attitudes towards obesity management in children. Approximately one-third of responders (GPs and parents) agreed that GPs did not have the necessary expertise, or the lack of financial incentive was an inhibiting factor in child weight management (Gage *et al.*, 2010). None of the UK-based studies investigated the role of pharmacological intervention for obesity treatment in their studies in children and young people.

A previous report showed that in the primary care, the majority of anti-obesity drugs were discontinued within 3 months of initiation, even before reasonable weight loss would be expected (Viner *et al.*, 2009). The reasons for this early discontinuation of anti-obesity drugs in young obese patients were unclear. Metformin has gained in popularity for obesity treatment in children and adolescents (Rogovik *et al.*, 2010). The current evidence suggests that orlistat and metformin are the two most commonly prescribed drugs for obesity treatment in children and adolescents (Matson & Fallon 2012; Petkar & Wright, 2013). Several studies have been carried out to explore health practitioners' views on childhood obesity management however most of the studies were conducted outside the UK. It is difficult to ascertain how generalizable the results from other countries are to the UK population. In addition, the research undertaken so far in this area has been limited to assessing the views of practitioners in general, and their experiences in prescribing anti-obesity drug to young people have not been explored in detail. As a result, orlistat and/or metformin prescribing to treat young people with obesity across primary care and secondary care were examined through a questionnaire survey.

6.2. Aims and objectives:

The aim of this chapter was to evaluate clinicians' experiences and attitudes toward prescribing anti-obesity drug to obese young people in their clinical practice through questionnaires to patients' GPs. There were four specific objectives:

1) To gain better understanding of GP experiences on prescribing anti-obesity drug treatments to young people
2) To gain better understanding of GP knowledge and skills on prescribing anti-obesity drugs
3) To gain understanding of reasons for anti-obesity drug discontinuation.
4) To identify key elements for future prescribing guide or intervention to support anti-obesity drug prescribing in clinical practice

6.3. Method:

6.3.1. Data source

Data from The Health Improvement Network (THIN) database were used to identify patients who received anti-obesity drug treatment. THIN covers approximately 5.7% of the UK population with 3.6 million active patients from 464 general practices (Cogedim Strategic Data Medical Research UK 2009). The practices included in the database are broadly representative of practices in the UK in respect of patients' demographics and characteristics (Murray *et al.,* 2013). GP surgeries participating in THIN are trained to use and enter medical records using the Vision general practice system (In Practice Systems; London, UK) (McCarthy *et al.,* 2013). Drugs are coded in the database using MULTILEX® codes (First DataBank; THIN). Diagnoses and symptoms are coded using READ code, a comprehensive hierarchical system (Chisholm 1990). Previous studies have confirmed the representativeness of the THIN population and the validity of diagnoses recorded in THIN (Lewis *et al.,* 2007; Ruigómez *et al.,* 2010). Prescription records within THIN are considered to be complete and accurate (Langley *et al.,* 2010; McCarthy *et al.*, 2012a,b; Murray *et al.*, 2013). The questionnaire study is an additional validation service provided by THIN's Additional Information Service (AIS) to assist researchers who require more detailed information that was not available from information recorded in the medical records.

6.3.2. Patient identification

Patients who had a prescription record of either orlistat or metformin on the THIN database during the study period 31st May 2010 to 31st May 2012 were identified. This sampling timeframe provided the most recent data available at the time the study was initiated in April 2012. As the purpose of this study was to explore GPs' experiences and opinions on medication used in obese young people, of those patients identified above, only those aged 18 years or under during the study period were included.

6.3.3. Questionnaire design and distribution

The investigator YingFen Hsia in conjunction with Dr Billy White (a clinical research fellow), Dr Russell Viner (a consultant paediatrician), Dr Sonia Saxena (a general practitioner) and Prof Ian Wong (a pharmacoepidemiologist) design the questionnaires. YingFen Hsia entered and analysed the returned questionnaires. The questionnaire was designed to cover the following outcome of interests:

1) Patients' demographic details such as gender, year of birth, type of anti-obesity drug received, ethnicity, co-morbidities.
2) Whether GP received advice from secondary/tertiary care team before the drug was initiated for obesity treatment; which assessment had been carried out before drug was initiated.
3) GP's experiences and opinion towards anti-obesity drug use for their patients.
4) One question asked specifically how competent GPs felt towards prescribing orlistat or metformin in both adults and children. This question was scored on 10-point Likert scale (one being not confident and 10 being very confident).
5) There was one open-ended question asking GPs' opinions on developing a guide to support anti-obesity drug prescribing in clinical practice.

The final 14-item questionnaire was designed in a check box format. Respondents (GPs) were also given a choice to provide additional information using free text. For most questions, respondents were able to provide more than one answer.

The questionnaire was sent to GPs by THIN's AIS, a research company licensed to contact GPs for research purposes. The questionnaires were only administered to GPs in practices that were willing to participate in THIN research studies. The THIN staff contacted GPs up to three times over a 3 month period. Investigators did not contact patients or GPs directly to maintain confidentiality. The THIN staff printed out the questionnaires and sent them directly to GPs. All selected patients in the database had a unique patient identifier (patient ID code and encrypted practice ID code). The unique patient ID enabled the GP to identify the patient(s). Each GP was requested to complete the questionnaire for their patient(s) and send questionnaires back to THIN. The THIN staff ensured that full confidentiality of the GP practices and patients were maintained throughout the questionnaire data collection and return of results to the research group. Any personal information that could disclose doctor' or patient's identity was removed before forwarding a copy of the questionnaire to researchers. The original questionnaires were retained in the THIN. GPs received a payment for each questionnaire completed (£100).

6.3.4.Data handling

Returned questionnaires were anonymised and inputted into two Microsoft Access (Microsoft Corporation, Washington, US) databases for first and second entry by YingFen Hsia. Double entry was for data cleaning purposes and also checked for internal consistency. The two Access databases were then imported into Stata/SE version 11.0 (Stata Corp, College Station, Texas, United States) to check any discrepancies. Each discrepancy identified was examined using the original questionnaire as a reference. YingFen Hsia conducted all the analyses of the returned questionnaires.

6.3.5.Data analyses

The overall aim of this study was to provide descriptive information on the current practices in childhood obesity treatment in primary care so descriptive statistics were used for each question in this survey study. Categorical variables were described as frequencies and percentages. Outcomes were tested for normality by using Kolmogorov-Smirnov tests. Continuous variables were reported using means and standard deviations (SD) for normally distributed variables and median and inter-quartile range (IQR) for non-parametric distributions. The drug treatment duration was calculated from the reported "date of first prescription" and "date of last prescription" in the questionnaires. Likert item scores were examined using Wilcoxon rank-sum test to investigate the confidence between prescribing medication to adults and children. Responses to the one open-ended question which asked about development of a guide to support drug prescribing in clinical practice were explored for common themes. Thematic analysis, a qualitative research technique, was used to identify the recurring terms, statements or comments in the responses and organised into prospective categories (Braun & Clarke 2006). Results were also presented by individual drug. For each question, the responses were analysed in respect of the numbers of questionnaires where the information for that question were completed by the GP.

6.3.6.Ethical approval

The National Health Service NRES Committee London- Surrey Borders Research Ethics Committee (REC reference: 11/LO/1020) granted ethnical approval for this study.

6.4.Results

A total of 151 patients were identified to receive orlistat or metformin between 31st May 2010 and 31st May 2012 (study period) in the database. One hundred and fifty-one questionnaires were sent to those patients' GPs across the UK (England, Wales, Northern Ireland, and Scotland); 121 GP-completed questionnaires were returned. Of the 121 patients, GPs returned 2 questionnaires for 6 of the patients as they had been receiving both orlistat and metformin during the study period. The response rate was high, with 80.1% (121/151) of the questionnaires returned. Only questionnaires in which the GPs confirmed their patient(s) received orlistat and/or metformin were considered valid for the study and were included in the final analyses. A flow chart of the process of identifying valid questionnaires is presented in Figure 1. A total of 114 GP-completed questionnaires were included in the final analyses in this study, though not all of the questions were answered on all of the questionnaires.

The demographics of the patients are presented in Table 6.2. Of the 114 patients, 98 were female patients (86.0%) and 16 were male patients (14.0%). There were marginally more patients receiving orlistat (53.5%; n=61) than metformin (51.8%; n=59). The median age at first drug prescription was 17 years (IQR: 16-18) for female patients and 16 years (IQR: 14-17) for male patients. Five patients received both orlistat and metformin at different time periods during our study period. The majority of respondents lived in England, of which 20 (17.5%) were from the West Midlands and 17 from London (14.9%; 17/114). Thirteen patients were from Wales (11.4%; 13/114), 9 patients (7.9%; 9/114) were from Scotland, and 5 patients from Northern Ireland (4.8%; 5/114). The majority of patients were reported as White (78/114; 68.4%), although for nearly 20% of the patients (22/114; 19.3%) ethnicity was not specified.

From GP reported duration, the mean duration of orlistat use was 1.7 months (IQR 0.5-8.5 months) and 13.9 months (IQR 4.0-24.1 months) of metformin use. Of these 114 patients, only 68 patients (59.6%) had more than one weight and height measurement in the returned questionnaires. The summaries of GPs' opinions and experiences on prescribing orlistat or metformin to their patients are presented in Table 6.3. Approximately 79% (48/61) of patients who received orlistat prescribed by their GPs without advice from secondary/tertiary care, whereas only 29% (17/59) of patients received metformin prescribed by GPs without advice from secondary or tertiary care. This indicates that specialists from secondary/tertiary care initiated the majority of metformin prescriptions for obese young people.

Figure 6.1: Flow diagram to identify valid questionnaires

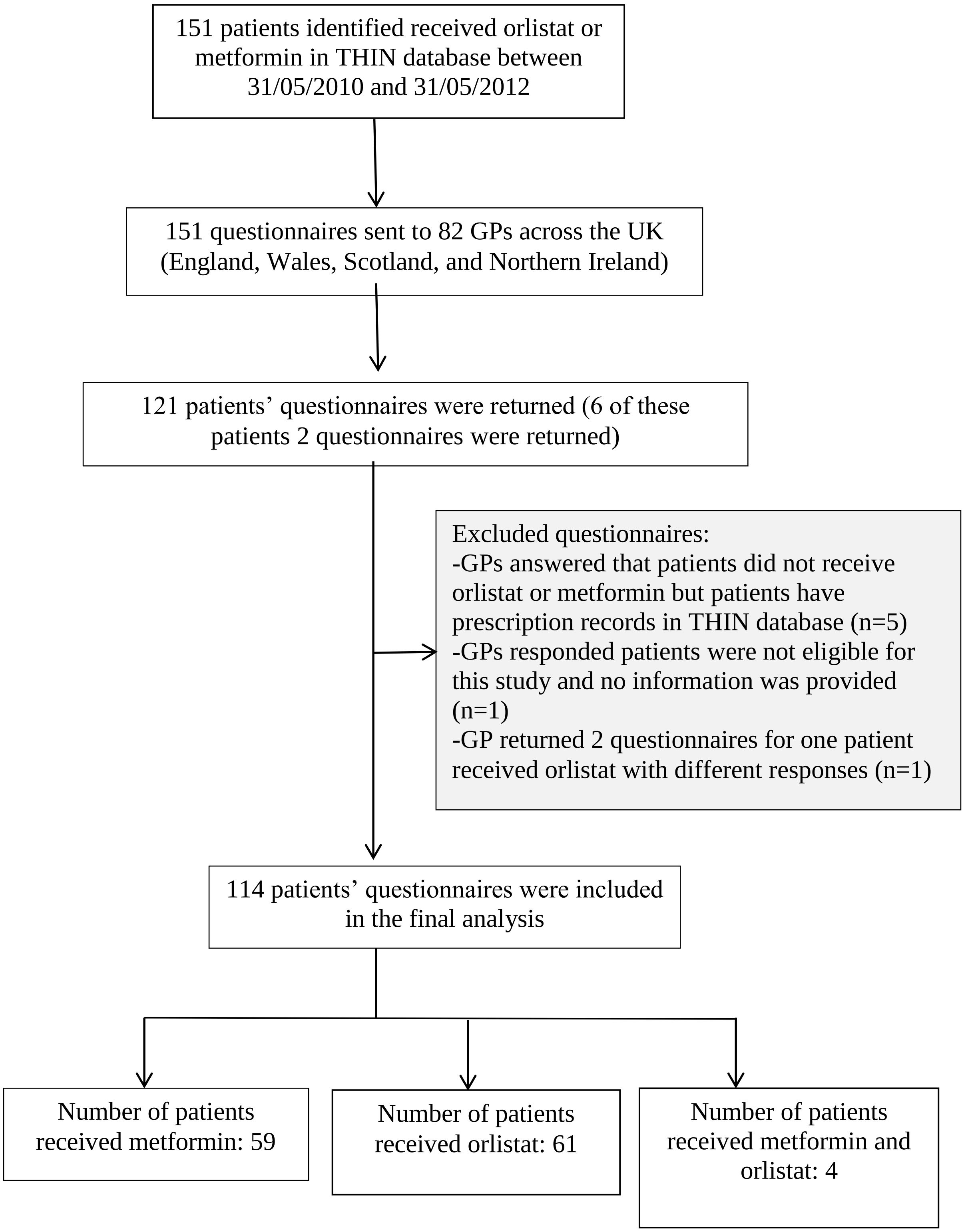


Table 6.2: Patient demographics in returned questionnaires

Patient demographics	**Total number of patients (n=114)**
Gender	
Female	98 (86.0%)
Male	16 (14.0%)
Medication use	
Median age (years) at 1st anti-obesity drug for female	17 (IQR: 16-18)
Median age (years) at 1st anti-obesity drug for male	16 (IQR: 14-17)
Number of patients received 1 anti-obesity drug	109 (95.6%)
Number of patients received more than 1 anti-obesity drug	4 (3.5%)
Number of patients received orlistat	61 (53.5%)
Number of patients received metformin	59 (51.8%)
Country	
England (by old NHS Strategic Health Authorities)	
East of England	7 (6.1%)
North East	3 (2.6%)
North West	13 (11.4%)
South Central	15 (13.5%)
South East Coast	7 (6.1%)
South West	3 (2.6%)
West Midlands	20 (17.5%)
Yorkshire & Humber	2 (1.8%)
London	17 (14.9%)
Wales	13 (11.4%)
Scotland	9 (7.9%)
Northern Ireland	5 (4.8%)
Reported ethnicity	
White	78 (68.4%)
Non-White	
Asian	2 (1.8%)
British African	1 (0.9%)
British Pakistani	3 (2.6%)
Caribbean	1 (0.9%)
Greek	1 (0.9%)
Indian	2 (1.8%)
Iranian	1 (0.9%)
Turkish	1 (0.9%)
Mixed	2 (1.8%)
Unknown	22 (19.3%)

Abbreviations: IQR, inter-quartile range; NHS, National Health Service. *Strategic Health Authorities (SHAs): SHAs were organisations within the NHS in England that were responsible for developing and improving health services in their local areas (http://www.mstrust.org.uk/atoz/sha.jsp).

Table 6.3: GPs' responses to each question on obesity treatment in young people

Questions	Orlistat	Metformin	Total
1. Question: What co-morbidities has this patient had?*	Number of respondents: 41	Number of respondents:43	Number of respondents: 84
Hypertension	0 (0%)	1 (2.3%)	1 (1.2%)
Hyperinsulinemia	0 (0%)	0 (0%)	0 (0%)
Dyslipidaemia	2 (4.9%)	1 (2.3%)	3 (3.6%)
Type 2 diabetes	3 (7.3%)	0 (0%)	3 (3.6%)
Psycho-social distress (e.g. low self-esteem, teasing and bullying)	12 (29.3%)	4 (9.3%)	16 (19.0%)
Mental and behavioural disorders†	13 (31.7%)	10 (23.3%)	23 (27.4%)
Weight-related exacerbations of conditions such as asthma	7 (17.1%)	3 (7.0%)	10 (11.9%)
Polycystic ovarian syndrome	7 (17.1%)	32 (74.4)	39 (46.4%)
Metabolic syndromes‡	0 (0%)	4 (9.3%)	4 (4.8%)
Orthopaedic/mobility issues related to weight	3 (7.3%)	2 (4.7%)	5 (6.0%)
Others	7 (17.1%)	2 (4.7%)	9 (10.7%)
2. Question: How was this medication initiated?			
Q2.1: GP issued this medication without secondary/tertiary care advice	Number of respondents: 48	Number of respondents: 17	Number of respondents: 65
Which of the following did the patient receive before initiation of medication?			
A. General assessment*:			
1) Dietetic review	22 (45.8%)	6 (35.3%)	28 (43.1%)
2) Lifestyle review	36 (75.0%)	8 (47.1%)	44 (67.7%)
3) Medical causes of obesity	16 (33.3%)	4 (23.5%)	20 (30.8%)
4) Growth and pubertal status	7 (14.6%)	4 (23.5%)	11 (16.9%)
5) Family history of obesity and co-morbidities	11 (22.9%)	3 (17.6%)	14 (21.5%)
6) Records inadequate to answer	8 (16.7%)	6 (35.3%)	14 (21.5%)
B. Assessment of any co-morbidities*:			
1) Hypertension	12 (25%)	2 (11.8%)	14 (21.5%)
2) Hyperinsulinemia	4 (8.3%)	0 (0%)	4 (6.2%)
3) Dyslipidaemia	6 (12.5%)	0 (0%)	6 (9.2%)
4) Type 2 diabetes	8 (16.7%)	3 (17.6%)	11 (16.9%)
5) Sleep apnoea	0 (0%)	0 (0%)	0 (0%)
6) Exacerbations of conditions such as asthma	5 (10.4%)	2 (11.8%)	7 (10.8%)
7) Psycho-social distress (e.g. low self-esteem, teasing, bullying)	12 (25.0%)	4 (23.5%)	16 (24.6%)
8) Mental health (e.g. depression, eating disorder)	9 (18.8%)	3 (17.6%)	12 (18.5%)
9) Records inadequate to answer	13 (27.1%)	4 (23.5%)	17 (26.2%)
C. Motivation review:			
1) Review of willingness and motivation to change	31 (64.6%)	13 (76.5%)	44 (67.7%)
2) Records inadequate to answer	14 (29.2%)	2 (11.8%)	16 (24.6%)
D. Other treatment options attempted*:			
1) Mental/emotional health support	11 (22.9%)	5 (29.4%)	16 (24.6%)
2) Exercise prescription	9 (18.8%)	5 (29.4%)	14 (21.5%)
3) Structured community intervention (e.g. MEND)	3 (6.3%)	0 (0%)	3 (4.6%)
4) Records inadequate to answer	12 (25%)	1 (5.9%)	13 (20.0%)

Table 6.3 Continued

Questions	Orlistat	Metformin	Total
Question: How was this medication initiated?	Number of respondents: 6	Number of respondents: 34	Number of respondents: 40
Q2.2: GP issued this medication after advice from secondary/tertiary care team			
A. Who recommended starting this medication?			
1) Paediatrician	3 (50.0%)	18 (52.9%)	21 (52.5%)
2) Adult physician	1 (16.7%)	4 (11.8%)	5 (12.5%)
3) Other (please specify)	2 (33.3%)	12 (35.3%)	14 (35.0%)
B. Was this practitioner part of a multi-disciplinary team with expertise in managing obesity in this age group?			
1) Yes	1 (16.7%)	7 (20.6%)	8 (20.0%)
2) No	3 (50.0%)	19 (55.9%)	22 (55.0%)
3) Don't know	2 (33.3%)	8 (23.5%)	10 (25.0%)
C. Did patient require support from primary care with this medication?*			
1) Yes: side effect	0 (0%)	1 (2.9%)	1 (2.5%)
2) Yes: efficacy	2 (33.3%)	4 (11.8%)	6 (15.0%)
3) Yes: other (please specify)	2 (33.3%)	4 (11.8%)	6 (15.0%)
4) No	1 (16.7%)	19 (55.9%)	20 (50.0%)
5) Don't know	0 (0%)	6 (17.6%)	6 (15.0%)
3. Question: What is the current status of this medication?	Number of respondents: 57	Number of respondents: 48	Number of respondents: 105
1) New prescription issued within last 3 months	4 (7.0%)	25 (52.1%)	29 (27.6%)
2) Patient stopped taking/ not requested prescription for more than 3 months. Please specify reasons if known	51 (89.5%)	21 (43.8%)	72 (68.6%)
3) Medication stopped by doctor. Why?	2 (3.5%)	2 (4.2%)	4 (3.8%)
a) Lack of efficacy	2	0	2
b) Non-concordance	0	1	1
c) Adverse effects	0	0	0
4. Question: Were any nutritional/vitamin supplement prescribed? *	Number of respondents: 58	Number of respondents: 47	Number of respondents: 105
1) No	56 (96.6%)	45 (95.7%)	101 (96.2%)
2) Yes, please specify	2 (3.4%)	2 (4.3%)	4 (3.8%)
5. Question: Who reviewed the patient to assess effectiveness, adverse effects and adherence? *	Number of respondents: 57	Number of respondents: 47	Number of respondents: 104
1) GP	36 (63.2%)	21 (44.7%)	57 (54.8%)
2) Paediatrician	2 (3.5%)	16 (34.0%)	18 (17.3%)
3) Adult physician	1 (1.8%)	3 (6.4%)	4 (3.8%)
4) Other (please specify)	13 (22.8%)	10 (21.3%)	23 (22.1%)
5) Don't know	11 (19.3%)	6 (12.8%)	17 (16.3%)
6. Question: Were there any adverse effects of this drug?	Number of respondents: 57	Number of respondents: 47	Number of respondents: 104
1) No	36 (63.2%)	35 (74.5%)	71 (68.3%)
2) Yes (please specify)	0 (0.0%)	2 (4.3%)	2 (1.9%)
3) Don't know	21 (36.8%)	10 (21.3%)	31 (29.8%)

Table 6.3 Continued

Question	Orlistat	Metformin	Total
7. Question: Did the patient's weight change while on the medication?	Number of respondents: 57	Number of respondents: 46	Number of respondents: 103
1) Loss	23 (40.4%)	12 (26.1%)	35 (34.0%)
2) Neutral	6 (10.5%)	11 (23.9%)	17 (16.5%)
3) Gain	5 (8.8%)	8 (17.4%)	13 (12.6%)
4) Don't know	23 (40.4%)	15 (32.6%)	38 (36.9%)
8. Question: Do you think this medication benefitted the patient?	Number of respondents: 56	Number of respondents: 47	Number of respondents: 103
1) Yes	9 (16.1%)	13 (27.7%)	22 (21.4%)
2) No	20 (35.7%)	10 (21.3%)	30 (29.1%)
3) Unsure	27 (48.2%)	25 (53.2%)	52 (50.5%)
9. Question: Metformin only: what was the indication for prescribing metformin? *	Number of respondents: 0	Number of respondents: 46	Number of respondents: 46
1) Diabetes	NA	0 (0%)	0 (0%)
2) Polycystic ovarian syndrome	NA	35 (76.1%)	35 (76.1%)
3) Insulin resistance/hyperinsulinemia	NA	9 (19.6%)	9 (19.6%)
4) Impaired glucose tolerance/impaired fasting glucose	NA	4 (8.7%)	4 (8.7%)
5) Obesity with none of the above	NA	2 (4.3%)	2 (4.3%)
6) Other: please specify	NA	0 (0%)	0 (0%)
10. Question: What tools were used to support the prescribing of this medication? *	Number of respondents: 43	Number of respondents: 34	Number of respondents: 77
1) NICE guidance	20 (46.5%)	7 (20.6%)	27 (35.1%)
2) MIMS**	1 (2.3%)	0 (0%)	1 (1.3%)
3) BNF	19 (44.2%)	7 (20.6%)	26 (33.8%)
4) GP notebook	5 (11.6%)	5 (14.7%)	10 (13.0%)
5) Local prescribing recommendations	9 (20.9%)	11 (32.4%)	20 (26.0%)
6) Others	3 (7.0%)	14 (41.2%)	17 (22.1%)
11. Question: How confident do you feel about prescribing anti-obesity medications using a scale 1-10 (10= very confident)			
To adults:	Number of respondents: 51	Number of respondents: 44	Number of respondents: 95
Score range	2-10	4-10	2-10
Mean score (SD)	7.9 (1.8)	8.1 (1.4)	8.0 (1.6)
Median score (IQR)	8 (7-9)	8 (8-9)	8 (8-9)
To children:	Number of respondents: 48	Number of respondents: 45	Number of respondents: 93
Score range	0-8	0-10	0-10
Mean score (SD)	3.3 (2.5)	3.8 (2.8)	3.6 (2.6)
Median score (IQR)	3.5 (1-5)	3 (2-6)	3 (2-5)
Other comments (GP did not score the scale)	1 GP: on advice of specialist	2 GPs : would not prescribe	3 GPs did not give score

Abbreviations: *Respondents could choose more than one answer NICE, National Institute for Health and Clinical Excellence; MIMS, the Monthly Index of Medical Specialities; BNF, British National Formulary; GP, general practitioner; NA: not applicable; SD, standard deviation; IQR, interquartile range. MEND: Mind, Exercise, Nutrition, Do it. MEND is an obesity prevention and treatment programme in the UK. ** MIMS is a national medical resource to provide healthcare professional with information on prescription medicines every month. † Mental and behavioural disorders include: depression, eating disorder, learning difficulty, speech and language disorder, autism, attention deficit hyperactivity disorder (ADHD). ‡Metabolic syndromes include: insulin resistance, impaired glucose tolerance.

Co-morbidities

A total of 50 patients (43.8%; 50/114) reported 1co-morbidity and 29 (25.4%) with ≥2 co-morbidities. The two most frequently reported co-morbidities in the orlistat treated group were: mental and behavioural disorders (31.7%; 13/41) and psycho-social distress (29.3%; 12/41). PCOS was the most frequently reported co-morbidity in the metformin treated group (74.4%; 32/43) followed by mental and behavioural disorders (23.3%; 10/43).

Prescribing medication for obesity treatment

GPs were asked whether they received advice from a secondary or tertiary care team before issuing a prescription for orlistat and/or metformin to their patients. A total of 74.5% (105/141) GPs responded. More GPs (61.9%; 65/105) replied that they did not receive advice from a specialist team compared to those GPs (38.1%; 40/105) who did.

1) GP issued medication without secondary/tertiary care team advice

Over half of GPs (61.9%; 65/105) responded that they issued medication to their patients without secondary or tertiary care team advice. Of these 65 GPs, 48 GPs prescribed orlistat and 17 prescribed metformin to their patients. This shows that more GPs initiated orlistat prescriptions without specialist advice, whereas more GPs prescribed metformin with advice from secondary or tertiary care. Overall, the most frequently reported general assessments made before patients received medication for treatment of obesity were: lifestyle review (67.7%; 44/65), dietetic review (43.1%; 28/65), and medical causes of obesity (30.8%; 20/65. Seventeen GPs (26.2%; 17/65) responded to the "Records inadequate to answer" for co-morbidity assessment. The most commonly reported co-morbidities GPs assessed were: psycho-social distress (24.6%; 16/65), hypertension (21.5%; 14/65), mental health (18.5%; 12/65), and type 2 diabetes (16.9%; 11/65). For the motivation review, the majority of GPs (67.7%; 44/65) responded that they would review patients' willingness and motivation to change before prescribing orlistat/metformin. "Mental/emotional health support" (24.6%; 16/65) and "Exercise prescription" (21.5%; 14/65) were the most frequently reported other treatment options that had been offered. However, nearly one quarter of GPs (20.0%; 13/65) responded "Records inadequate to answer".

2) GP issued medication with secondary/tertiary care team advice

Forty GPs (38.1%; 40/105) responded they received advice from a secondary or tertiary care team before prescribing medication to their patients. The majority (85.0%; 34/40) answered that they prescribed metformin after receiving advice from specialists in secondary/tertiary care team. GPs were asked who recommended starting the medication. The frequently reported specialist was paediatrician (21/40; 52.5%). Fourteen GPs responded “Other (please specify)” but only 10 of them provided additional information; 5 gynaecologists and 2 endocrinologists who recommended metformin while 1 gynaecologist and 1 dietician recommended orlistat. One GP responded that the recommendation to prescribe orlistat came from the lipid clinic.

GPs were asked if prescribers were part of a multi-disciplinary team with expertise in managing obesity in young people. Over more than half of GPs (55.0%; 22/40) answered they were not part of a multi-disciplinary team that managed obesity in this age group. Half of the GPs (50.0%; 20/40) responded that patients did not require support from primary care with their medication treatment while only 13/14 reported that the patients needed support. 1 GP responded “Yes: side effect” for metformin treatment. Four GPs responded “Yes: efficacy” for metformin treatment and 2 ‘efficacy’ for orlistat treatment. Six GPs responded “Other (please specify)” and 4 GPs provided additional information. Of these 4 GPs, one responded that supervision for metformin treatment was required. There were three responses that patients required support from primary care for: weight (n=1), psychological (n=1), and medication (n=1) in the orlistat treated group.

Current status of medication treatment

GPs were asked the current status of medication treatment for their patients at the time of questionnaire completion. There was a clear difference between the orlistat and the metformin treated patients. For the orlistat treated group, the majority of GPs (89.5%; 51/57) responded that patient had stopped taking orlistat or had not requested a prescription for more than 3 months in the orlistat treated group. Over half of GPs (52.1%; 25/48) responded that a new prescription was issued within the last 3 months in the metformin treated group. GPs were further asked if medication was stopped by a doctor and the reason for treatment discontinuation. Two GPs responded that medication was stopped by a doctor because of “Lack of efficacy” in the orlistat treated group. Two GPs responded that metformin was stopped by a doctor but only one GP answered “Non-concordance”. None of the GPs responded that medication stopped by a doctor was due to “Adverse effects” for this question.

Nutritional or vitamin supplement prescribing

The vast majority of GPs (96.2%; 101/105) stated that patients did not receive any nutritional or vitamin supplement at the time they received orlistat or metformin treatment. One GP stated that the patient received orlistat along with multivitamin OTC (Over The Counter) and another answered that the patient received vitamin D with orlistat treatment. In the metformin treated group, 2 GPs answered, “Yes” but details were provided.

Who reviewed the patient to assess effectiveness, adverse effects and adherence?

In general, GPs (54.8%; 57/104) were the most common healthcare professional to review patients’ medication treatment. In the metformin treated group, 16 GPs (34.0%; 16/34) stated that paediatricians reviewed patients’ medication treatment while only 2 GPs (3.5%; 2/57) responded that a paediatrician reviewed treatment in orlistat group. A total of 23 GPs (22.1%; 23/104) answered “Other, please specify”. Of these 23 GPs, 17 (22.1%; 17/23) provided information regarding treatment review and the remaining 2 GPs did not give additional information. In the metformin treated group, 3 GPs responded gynaecologist, 1 responded dietician, 1 responded endocrinologist, and 1 responded patient did not attend for review. Three GPs responded that the practice nurse reviewed orlistat treatment, one responded that patient was not seen again for 9 months, one responded that patient stopped attending and only had one prescription, and 4 responded that patients did not attend follow-up.

Adverse effects of drug treatment

GPs were asked whether there were any adverse effects of drug treatment. Overall, more than half of GPs (68.3%; 71/104) responded “No” to this question. Approximately 30% of GPs (31/104) answered, “Don’t know”. Two GPs reported adverse effects of nausea (n=1) and diarrhoea (n=1) to metformin treatment.

Weight change during orlistat or metformin treatment

GPs were asked about weight loss in patients who received medication. Overall, approximately 36.9% (38/103) of GPs stated they did not know whether their patients' weight changed while on medication. In the orlistat treated group, approximately 40% of GPs (n=23; 23/57) responded they did not know if their patients' experienced weight change. Twenty-three GPs (40.4%; 23/57) answered that their patients lost weight while on orlistat; of these, 17 provided weight loss information. Eleven patients experienced weight reduction from 2kg to 5kg, 5 patients lost between 7 kg and 10kg, and 1 patient had a weight loss of 22kg. One GP responded that a patient "lost one stone on WW (Weight Watchers)". Two GPs responded that their patients gained 2kg whilst on orlistat for obesity treatment.

In the metformin group, 12 GPs (26.1%; 12/46) stated that their patients lost weight while on treatment. Of these, only 6 GPs provided detailed weight loss data. Two GPs stated that their patients lost 4kg and 6kg body weight. Four GPs responded that their patients lost weight range from 6kg to 12kg. Eight GPs stated that their patients gained weight when they received metformin treatment but only 5 GPs gave details about the weight gain. Of these 3 responses: 1 patient gained 1.5 kg, and 2 patients gained 9kg and 10kg when they received metformin treatment. The remaining 2 GPs' responses were: 1 patient "gained weight but was not compliant" and 1 patient's "BMI increased".

The benefit of medication treatment

In response to the question about whether their patients benefited from medication treatment, overall half of GPs (50.5%; 52/103) were "Unsure". According to the responses, 35.7% (20/56) of patients on orlistat and 21.3% (10/47) on metformin did not benefit from treatment. Approximately 27% (13/47) of patients experienced the benefits of metformin. Only 16% (9/56) of patients experienced the benefit of orlistat treatment on weight loss.

Tools to support the prescribing of medication in primary care

GPs were asked which tools they used to support medication prescribing. Twenty GPs (46.5%; 20/43) used NICE guidelines and BNF (44.2%; 19/43) to support orlistat prescribing. Compared to orlistat, less GPs used NICE and BNF when prescribing metformin. For the metformin group, most GPs responded "Others" (41.2%; 14/34) and "Local prescribing recommendation" (32.4%; 11/34). Of the 14 GPs who responded with "Others", 4 answered, "Don't know". The remaining 10 GPs provided additional information including: "recommended by consultant" (n=3), "endocrinologist" (n=1), "gynaecologist" (n=1), "ask paediatrician" (n=1), "specialist advice" (n=1), "given by locum" (n=1), "previous knowledge" (n=1), and "not recorded, too long ago" (n=1).

Indications for prescribing metformin

GPs were asked the indications for which metformin was prescribed to their patients. The two main indications for prescribing metformin were "Polycystic ovarian syndrome" (76 %; 35/46) and "Insulin resistance/hyperinsulinemia" (19.6%; 9/46). Only 2 GPs (4.3%; 2/46) answered "Obesity with none of the above".

GP's confidence regarding prescribing medication for obesity treatment in adults and children

GPs were asked to rank how confident they felt about prescribing anti-obesity medication using the scale from 1-10 (10= very confident). Overall, GPs felt more confident prescribing orlistat or metformin to adults than to children. Twelve GPs (12.5%; 12/96) stated "0" (not confident) in prescribing orlistat or metformin to children for obesity treatment. Although we asked GPs to score their confidence from 1 to 10, approximately 12% of GPs had scored 0 when scoring their confidence on prescribing medication to children in this question. Three GPs provided additional comments about their level of confidence in prescribing medication to children: 1 GP stated, "on advice of specialist" in the orlistat group, and 2 GPs "would not prescribe" in the metformin group.

Additional comments regarding prescribing drug for obesity treatment

GP were asked to give comments regarding prescribing drugs for obesity treatment. Thirty-two respondents in total supplied additional comments regarding their experiences and opinions on orlistat or metformin use for obesity treatment.

Comments on orlistat use for obesity treatment

Four GPs had no comments to this question. Fourteen GPs provided additional comments on prescribing orlistat for obesity treatment. We report here the general themes of these additional comments including: patients were not willing to continue drug treatment, patients did not attend clinic for follow-up assessment, and uncertainty about treatment effect.

"He was not keen to take it and probably did not take any since has defaulted from endocrinology follow up." (Questionnaire 23)

"Clearly patient was not keen to comply; more support needed?" (Questionnaire 42)

"Drug was initiated by FY2 (Foundation Doctor Year 2) or who no longer works here. Patient never returned" (Questionnaire 26)

"Inadequate counselling, no weight taken on day of prescription; did not attend follow up" (Questionnaire 131)

"Not sure value of lifestyle, drug" (Questionnaire 22)

"Only given one month unsure if used; told to avoid fatty foods and other measures trials beforehand." (Questionnaire 114)

"Not very effective from past experience; bloatedness and diarrhoea as side effect" (Questionnaire 39)

"I try to avoid whenever possible" (Questionnaire 129)
"Not good outcome and poor results." (Questionnaire 145)

"In this case, patient had already lost 1 stone in weight but struggling to lose more" (Questionnaire 111)

Other reported comments were not relevant to drug treatment in obesity management.

"Patient had gastric band" (Questionnaire 128)

"Mother had used" (Questionnaire 149)

Comments on metformin use for obesity treatment

The 16 responses about metformin use for obesity treatment were reviewed, of which 4 had no comment on metformin use for obesity treatment. There were some recurring themes: metformin was for PCOS treatment, prescribed by specialists, and not prescribed for weight loss. The following comments from respondents illustrate these points:

"Poor record keeping reply height/weight although was more for PCOS, patient had gone and read up on it. Had already joined weight watchers herself" (Questionnaire 10)

"Only for secondary care initiation" (Questionnaire 18)

"This drug was for PCOS, hair loss, insulin resistance recommended by paediatric endocrinologist" (Questionnaire 19)

"Not prescribed as anti-obesity" (Questionnaire 55)

"Prescribed by consultant" (Questionnaire 69)

"Probably prescribed on valid recommendation since after registration" (Questionnaire 75)

"This was prescribed for PCO. Wouldn't normally prescribe this just for weight loss" (Questionnaire 104)

"Metformin was used not just to help with weight but to help with amenorrhea and polycystic ovaries" (Questionnaire 151)

"Metformin for PCOS" (Questionnaire 155)

Few other responses on metformin treatment in obese young people as below:

"Is working well" (Questionnaire 78)

"Needs to know has weight loss is the prime effect of metformin" (Questionnaire 104)

“Unusual to prescribe metformin in this age group” (Questionnaire 155)

To develop guidelines to support clinicians in prescribing for obesity

A total of 65 responses to the open-ended question about developing guidelines to support clinicians in prescribing drugs to obese young people were reviewed. The majority of responses are positive comments on developing a guideline to assist with prescribing medication for obesity treatment in young people. In addition, respondents expressed what they would like included in the guideline. There were only 7 responses (10.8%; 7/65) that expressed no interest in developing a guideline. A number of themes emerge from these supporting comments including: drug information (e.g. indication, dose, side effect) in children, a clear and simple guide to follow, advice on other non-pharmacological interventions. Examples of responders’ comments representing the aforementioned themes are given as below:

Drug information:

“Prescribing indications criteria.” (Questionnaire 23)

“Indications, dose, regimen, side effects, outcomes.” (Questionnaire 36)
“Paediatric indication.” (Questionnaire 65)

“Indications, follow up, other investigations to consider.” (Questionnaire 35)

“Exclusion/contraindications. Safety advice. When to stop if not working.” (Questionnaire 59)

“Yes; age group and advice anti-obesity.” (Questionnaire 79)

“Age related prescribing.” (Questionnaire 82)

“Exclusion/contraindications. Safety advice. When to stop if not working.” (Questionnaire 59)

“Paediatrics advice.” (Questionnaire 91)

“Prescribing in <18 years.” (Questionnaire 92)

“Guidance for drug use, duration of use, monitoring, when to stop.” (Questionnaire 120)

“Indications” (Questionnaire 129)

“As OTC medication not sure an intensive team involvement is needed.” (Questionnaire 149)

“Side effects and risk.” (Questionnaire 150)

“Role of medication use.” (Questionnaire 151)

A clear and simple guide to follow:
“Clear stepwise instructions, criteria, and thresholds. Advice on continuing treatment when to *stop etc.”(Questionnaire 34)*

“Clear protocols on assessment before initiating anti-obesity drugs.” (Questionnaire 58)
“Protocol to follow easily.” (Questionnaire 116)

“Simple guideline. Frequency of follow up.” (Questionnaire 131)

“Clear advice please.” (Questionnaire 134)

“Clear concise guideline.” (Questionnaire 135)

“A flow diagram patients can have too” (Questionnaire 137; Questionnaire 139)

“Easy flow chart.” (Questionnaire 154)

“Clear guidance of when to start monitoring and when to stop it.” (Questionnaire 155)

Although we asked for opinions on developing a guideline for drug prescribing, some GPs expressed the need for non-pharmacological interventions to be included.

<u>*Advice on other non-pharmacological interventions:*</u>

"Emphasis on lifestyle advice as well as side effects on medication" (Questionnaire 18)

"What screening support and intervention should be used before treatment advice, monitoring and when to stop." (Questionnaire 74)

"Emphasis on non-drug treatment that is very important (diet/exercise/lifestyle) when to stop treatment." (Questionnaire 104)

"Advice on other measures to take beforehand or references/leaflet to give out." (Questionnaire 114)

"Others interventions to be used in conjunction with medication." (Questionnaire 124)

"Information about targets and investigation." (Questionnaire 127)

"Working with a group together and special clinic for monitoring and support for patients." (Questionnaire 145)

"Provide advice about lifestyle, eating and long term change." (Questionnaire 159)

6.5.Discussion

Summary of main findings

In the UK, GPs play an important role in managing childhood obesity in primary care. This study adds to the current understanding of the role of GPs in the treatment of this condition, including their prescribing of anti-obesity drugs, also their attitudes, and opinions regarding medication use in obesity management in young patients. We used data from a computerised UK primary care medical records database to identify patients under 19 years who had received orlistat or metformin. Questionnaires were sent to GPs of the patients identified, to explore GPs' experiences and elicit comments on prescribing orlistat and metformin. A high questionnaire response rate (80%; 121/151) was achieved in this study, which has also been reported (>95%) in previous studies using data from the THIN database (Lo Re V 3rd *et al*., 2009; Ruigomez *et al.,* 2010; McCarthy *et al.,* 2013). The high response rate may in part be due to the financial incentive given for return of a completed questionnaire. In addition, to contributing data to the THIN database, the GPs who participated in our study had also given consent to provide additional anonymised patient information for research purposes.

Details of different interventions (lifestyle, behavioural, physical activity, and also pharmacological) for obesity management in children are fully described in the NICE guidelines. Despite clear guidance that anti-obesity drugs should be started in a specialist paediatric setting before they can be continued in primary care (NICE 2006), our survey findings suggest that over half of GPs (61.9%; 65/105) did not receive specialist advice before initiating medication (orlistat or metformin). This prescribing practice is not in accordance with the NICE guidance. The questionnaire for the current study was administered in 2012; the data obtained related to the study period 2010 to 2012, a time when the NICE guidelines were already in place. The NICE guidelines provide comprehensive evidence that are quite lengthy, which may make it difficult for GPs or other healthcare professionals to read or implement in practice. A previous study found GPs and practice nurses in Glasgow did not routinely use weight management guidelines (the Scottish Intercollegiate Guidelines Network; SIGN), mainly due to lack of time (Mercer *et al.,* 2001). Similarly, a study in Bristol found that most GPs and practice nurses did not look at the NICE or the Department of Health guidance on childhood obesity management (Turner *et al.,* 2009). This may explain why, in our study, most GPs did not consult specialists' before initiating anti-obesity drug treatment.

It is interesting to note that most GPs initiated an orlistat prescription without seeking advice from specialists, whereas the majority of GPs consulted specialists before initiating a prescription for metformin. At present, metformin is not recommended for obesity treatment in national guidelines such as NICE or authoritative drug prescribing documents widely used in the UK (BNF; BNF Children; Summary of Product Characteristics). Few GPs reported that they prescribed metformin on the recommendation of specialists (e.g. paediatric endocrinologist). Possible reasons that GPs consult specialist' advice prior to starting treatment with metformin may be a lack of an authoritative guideline, and current limited evidence that supports use for obesity treatment in both adults and children. Over half of GPs in our study also expressed uncertainty about metformin efficacy on weight loss, especially for young people. This may also explain why most GPs felt incompetent to prescribe metformin for obesity treatment, especially in children. In addition to obesity treatment, metformin is commonly used for PCOS treatment in clinical practice. In contrast to metformin, several studies have shown the efficacy of orlistat along with lifestyle interventions in weight loss in adults and children in the past few years. Therefore, GPs may feel more confident about initiating orlistat for treatment of obesity in young people without advice from specialists.

Obesity is associated with a range of co-morbidities such as hypertension, diabetes, depression, and low self-esteem in young people (Viner *et al.,* 2006; Kimm *et al.,* 1997; Goodman *et al.,* 2002). Due to these obesity-related conditions, a range of healthcare professionals such as dieticians, endocrinologists, and psychologists will also be involved in obesity treatment for paediatric patients (Ogden & Flanagan 2008). In our study, of those GPs who reported that they contacted a specialist, the majority consulted a paediatrician for advice before initiating prescribing but some contacted other specialists such as gynaecologists, adult physicians, and endocrinologists have also been contacted for advice. However, over half of the specialist practitioners (52%) who provided GPs with advice were not part of a multi-disciplinary team with expertise in managing obesity in young people. The NICE guidelines state that an anti-obesity drug should only be prescribed to children by a multidisciplinary team with expertise in obesity management in this age range.

Orlistat inhibits pancreatic and gastric lipase by decreasing ingested triglyceride hydrolysis; consequently, it may impair absorption of fat-soluble vitamins (e.g. A, D, E, K). It is recommended that a multivitamin supplement (especially Vitamin D) be taken while patients are taking orlistat if there is concern about deficiency of fat-soluble vitamins (Summary of Product Characteristic *Orlistat* 2012; BNF Children). However, the data from our study showed that the vast majority of patients (96%) who received orlistat for treatment of obesity did not take a multivitamin supplement. This may be due to the lack of experience in prescribing medication to young people for obesity treatment. Many GPs felt more confident prescribing a drug for obesity treatment to adults compared to young people. GPs reported that nearly 90% of patients stopped taking or had not requested an orlistat prescription for more than 3 months. We have previously reported that only one-quarter of patients remained on orlistat treatment for longer than 3 months and the majority of patients discontinued treatment within the first 3 months (Viner *et al.,* 2009). Orlistat was approved in the UK to treat obesity and it has recognised and well established adverse event profile including (but not limited to) faecal urgency, liquid or oily stools, faecal incontinence, though gastro-intestinal effects can be minimised by reduced fat intake. According to GPs, 63% of patients did not experience adverse events and the remaining GPs did not know if patients had an adverse event associated with orlistat treatment. Only 1 GP provided information about adverse events (bloatedness and diarrhoea) that the patient experienced while on orlistat treatment. As for drug treatment effect, approximately 40% of GPs did not know their patients' weight change while on orlistat treatment. Approximately 48% of GPs were unsure whether their patients benefitted from orlistat treatment.

Approximately 74% of patients did not experience adverse events while receiving metformin treatment and more than half of the GPs (53.2%) were unsure about the effect of metformin treatment effect on weight loss in their patients, a higher proportion than for orlistat. In contrast to orlistat, more patients (52%) had new metformin prescription issued within last 3 months. Our study was not designed to estimate drug treatment adherence, but according to the patients' GP, the mean treatment duration of metformin was longer than that of orlistat. It may be that the majority of patients were issued metformin primarily for the treatment of PCOS and not for the treatment of obesity. Several GPs had commented that metformin was issued for PCOS for obesity treatment. This is consistent with a previous study in the UK, which used a longitudinal primary care database and demonstrated that PCOS was the main indication for metformin prescribing to female adolescents (Hsia *et al.,* 2012).

Most GPs in our study reported that they did not have adequate documentation on treatment outcome. For a number of the questions the GPs did not know the answers. This was particularly the case when GPs were asked their opinion on the benefits of medication treatment. Also, details of orlistat and metformin adverse events were not reported by the GPs. This could be because patients did not return for follow-up assessment or inadequate documentation in GPs' clinical records. Another study found that none of the practitioners (GPs, practice nurses, health visitors) were in regular contact with the obese children. The authors commented that even when practitioners offered follow-up appointments most patients did not return. One GP further expressed that they only saw a small proportion of obese young people who sought help from their GP (Turner *et al.*, 2009). In 2003, in order to reinforce good prescribing practice in all clinical settings, the Royal College of Physician of London published guidance on appropriate prescribing and management on anti-obesity drugs (Royal College of Physician of London 2003). It suggested that clear documentation is required when patients receive anti-obesity drugs for treatment. Also, the guidance recommended that there should be written notification to the patient's GP, if another physician initiated prescriptions. The information that should be documented included the reason for treatment, the dose and intended treatment duration, and possible untoward effects. The fact that GPs did not know the treatment outcome in many cases indicates that management practices for childhood obesity could be further improved.

To develop a new guide supporting anti-obesity drug treatment

Since the release of the NICE guideline on obesity management in young people in 2006, practitioners have been given specific guidance in assessing, treating, and preventing obesity in these patients. However, our data indicated that the current guideline does not fulfil its main objectives. A range of views was expressed by the GPs in our study on developing new guidance to support clinicians on drug prescribing for obesity treatment. Despite comprehensive guidance provided in the NICE guideline, in our study, GPs expressed their support for the development of a new guide for prescribing anti-obesity drug to young people. Some GPs also commented that recommendations on non-pharmacological interventions should be included in the new guideline. The current NICE guideline contains evidence-based literature on diet, exercise, and behavioural change approaches, and also drug treatment for management of obesity in childhood. The comments from GPs in our study again raised the question of how practical NICE guidelines are for practitioners to follow in their day-to-day practice. Previous studies have shown that practitioners rarely use NICE guidelines in their clinical practice (Mercer *et al.*, 2001; Turner *et al.*, 2009; Owen-Smith *et al.*, 2010). The study by Turner and colleagues (2009) found that only 3 practitioners had looked at the NICE obesity guideline (10%; 3/30) and that the remaining practitioners had never seen the guideline. Another recent study reported that some healthcare professionals did not trust the reliability of NICE guidance and so were less likely to implement these in practice. The comment from one GP was *"I think where we [GPs] perceive that NICE guidance has come up with politically correct statements. I think we are pretty sceptical and probably ignore it. For instance…prescribing of obesity medications….I don't think that's the right solution to those problems."* (Owen-Smith *et al.*, 2010). Similarly, the Glasgow study reported that the SIGN guidelines were clearly not used much amongst practitioners (GPs and practice nurses); who felt that the SIGN guidelines overly promoted the use of anti-obesity drugs (Mercer *et al.*, 2001). Several GPs in our study expressed the need to develop an easy and simple new guide to follow. Both NICE and SIGN guidelines are lengthy and detailed and it is not easy to implement these guidelines into clinical practice.

Strengths and limitations

To our knowledge, this is the first questionnaire survey used to assess GP's experiences in prescribing orlistat and metformin to young people for obesity treatment in UK primary care. The main strength of this study was that we utilised a large primary care health record database (THIN) that covers 5.7% of the UK population to examine GP's views on prescribing medication for obesity treatment to their young patients. Additionally, the questionnaires were sent to GPs across the UK so the results from the current study should be generalizable. GPs' experiences in prescribing orlistat and also metformin to young people for obesity treatment were examined, as no research in this area had been previously undertaken. Further, a high response rate was achieved in this study. There are a number of reasons that are likely to contribute to this high response rate; the GPs who contribute data to THIN database are a self-selected group, and those who completed and returned questionnaires were compensated. However, there are a number of limitations to this study.

Firstly, this study was conducted to understand GP's experiences of prescribing medication for obesity treatment in young people and so we did not examine which non-pharmacological interventions had been used in prior to or in addition to drug treatment. Secondly, we could not assess prescriptions initiated at secondary care because THIN only records prescriptions issued in primary care, excluding prescriptions dispensed in hospitals. Thus prescriptions that were prescribed in secondary care were not included in the present study. Thirdly, there were a high number of missing records in returned questionnaires. There was the varying response rate for individual questions. For a number of questions asked, the answers were not known by the GPs. We did not know whether the missing information/data were due to inadequate documentation in the practice. Fourthly, the assessment of the open comments in the questionnaire to ascertain common themes is subjective, as this open-ended question was included for exploratory purposes. The study was not intended to be a qualitative study. Finally, a limitation of most postal surveys is that of response bias and our study is not exempt although the response rate was high (about 80%). It may be that those who responded to the questionnaires were more interested in childhood obesity. A further limitation is that some GPs provided the weight and height measurements in the return questionnaire, but we did not intend to investigate treatment effect on orlistat or metformin. We primarily used this information to indicate the completeness of the recording of these measurements in primary care setting. There were many measurements (height, weight) that were not recorded in the returned questionnaires. We do not know whether these missing measurements were not documented or patients' weight and height were not measured at the GP practice.

Implication for practice and future research

Childhood obesity continues to be a problem in the UK. It is important to examine how practitioners are addressing this critical issue in order to identify the need for further training and services in clinical practice. The present study provides a timely and useful update of GPs' practice on prescribing medication for obesity treatment in young people. Results of this study will generate recommendations for clinical practice in childhood obesity management, which may further inform policy guidelines. Despite the current NICE guidelines, we have seen that clinical practitioners support the development of a prescribing guide on childhood obesity treatment. At present, the obesity indicator in the QOF scheme does not apply to young people aged under 16. To target successful childhood obesity management, children and adolescents should also be included in the QOF scheme. In addition, GPs should be offered further training and support on the appropriate anti-obesity drug to prescribe. A useful area for future research would be to explore patients' views on medication use for obesity management and the reasons for them to stop treatment.

6.6.Conclusion

The findings of this study show that GP's prescribing practices seem not to be in accordance with NICE guidance on the management of obesity in children and adolescents. More than half of GPs initiating medication did not receive advice from specialists in secondary care. Results in the study reveal that the majority of GPs have a lower level of confidence in prescribing anti-obesity drugs to young people compared to adults especially for prescribing metformin. About 89% of GPs supported and suggested there was a need to develop simple and easy guidance to assist them with prescribing anti-obesity drugs, and several of them also suggested that non-pharmacological interventions should be included in the guide. Over one-quarter of GPs did not know whether their patients had experienced any adverse drug reaction. In addition, more than one-third of GPs did not know their patients' treatment outcome while on drug treatment. This study highlights an urgent need to improve current practice in childhood obesity management in primary care.

Chapter 7 Overall Discussion and Conclusion

Prior to the commencement of this thesis, a number of gaps in the knowledge of anti-obesity drug use in children and adolescents were identified, gaps which this thesis sought to address. This thesis has increased the current knowledge of anti-obesity drug use in children and adolescents in primary care and secondary care in the UK. This thesis has systematically evaluated the efficacy and adverse drug reactions of anti-obesity drugs used in children and adolescents from published RCTs by utilising a systematic review and meta-analysis (Chapter 3). Pharmacoepidemiological studies utilising large health care databases (General Practice Research Database, IMS Disease Analyzer) have been performed to investigate anti-obesity drug prescribing patterns in children and adolescents in the primary care setting (Chapter 4). Also, a prospective cohort study was conducted to investigate drug prescribing patterns for obesity treatment in young people in secondary care. Further analysis of this study was performed to determine the effect of metformin treatment together with lifestyle intervention compared to lifestyle intervention alone, after 6 months of treatment (Chapter 5). To date, there is no research to assess GP's experiences in prescribing anti-obesity drugs to obese children and adolescents in the UK primary care. Thus, a GP questionnaire survey study was conducted to evaluate GP's experiences and attitudes in prescribing medication to young people for obesity treatment across the UK (England, Scotland, Wales, North Ireland) (Chapter 6). This final chapter summarises the main findings of these studies, including an overall discussion of the results of the studies, and recommendations for future research are given.

7.1.Summary of main findings

7.1.1.Systematic Review and meta-analysis of RCTs of anti-obesity drugs used in children and adolescents

A systematic review and meta-analysis of RCTs published between January 1996 and January 2008, was conducted to investigate the efficacy of licensed anti-obesity drugs (orlistat, sibutramine, rimonabant) and the reported ADRs in children and adolescents (aged $\leq$ 18 years). A total of 16 RCTs were appraised and assessed for inclusion in the meta-analysis: 6 RCTs for orlistat and 10 RCTs for sibutramine. Of these 16 RCTs, 2 studies of orlistat and 4 studies of sibutramine were included in the meta-analysis. No RCTs for rimonabant in this population were identified. The results from the 2 RCTs for orlistat showed that 6 months of treatment with orlistat together with behavioural support reduced BMI by 0.83 kg/m^2. The meta-analysis of the 4 RCTs for sibutramine demonstrated that with behavioural support, BMI was reduced by 2.20 kg/m^2. From a search of papers published from February 2008 to November 2011, conducted to update the systematic review, only one RCT of orlistat was identified, after the initial screening of the abstracts (Chanoine & Richard, 2011). As this study was an additional analysis from a previous study which had been included in our original review (Chanoine *et al*., 2005), we did not include it in the meta-analysis.

The results of the review are consistent with the results of previous systematic reviews (McGovern *et al*. 2008; Oude Luttikhuis *et al*. 2009). Each of the RCTs included in these reviews, demonstrated a statistically significant effective on weight loss of anti-obesity drug treatment in young people however, this benefit was not always of clinical significance. These two systematic reviews by McGovern *et al*., (2008) and Oude Luttikhuis *et al*. (2009) did not undertake a meta-analysis of ADRs on orlistat and sibutramine. In reviewing the ADRs reported in the RCTs, the most frequently reported ADRs are those that are included in the SPCs. In this review, the frequency of reported gastrointestinal ADRs to orlistat was high compared to the placebo groups. Sibutramine was found to increase systolic and diastolic blood pressure.

Evidence from the short-term (6 months) RCTs in children and adolescents, support the benefit of anti-obesity drugs as an adjunct to lifestyle interventions (e.g. behavioral support, exercise, diet). At present, the long-term (e.g. over 1 year treatment) effectiveness and risk of these drugs in young people is lacking as no long-term RCTs have been published in this population. In contrast, the benefits of long-term use of orlistat and sibutramine in adults have been well-documented. Li *et al*., (2005) and Rucker *et al*., (2007) reported the efficacy of long-term (over 1 and/or 2 years) treatment with orlistat or sibutramine in adults, from RCTs. A systematic review of 4 RCTs has shown a significant effect of rimonabant on weight loss in adults (Curioni & André, 2006). However, this drug was not recommended in NICE guideline (2006) on the treatment of obesity in young people. In January 2010, the NICE revised the 2006 obesity management guideline after the withdrawal of sibutramine. Orlistat is currently the only drug recommended for obesity treatment in young people with certain caveats (e.g. severely life-threating co-morbidities). Further research is required to determine the long-term effects of orlistat for the treatment of obesity in this population.

7.1.2.Prescribing patterns of anti-obesity drugs in children and adolescents in primary care

The use of the GPRD database (a primary care database) enabled us to study a large cohort of young people who had received orlistat, rimonabant, or sibutramine, and to follow them over a period of several years. In terms of prescribing patterns, orlistat was the most frequently prescribed drug for the treatment of obesity in young people between January 1999 and December 2006 (study period). In contrast, there was only one prescription for rimonabant issued during the study period. After the introduction of orlistat and sibutramine to the UK market in 1999 and 2001, respectively, the overall annual prevalence of prescribing of these drugs to children and adolescents increased 15-fold from 0.006 per 1000 patient-years in 1999 to 0.091 per 1000 patient-years in 2006.

In this study if no further prescription was issued within 90 days (3 months) of the end of the previous prescription, treatment was considered to be discontinued. An unexpected finding from this study was that approximately 45% of orlistat prescriptions and 25% of sibutramine were discontinued after only one month. The majority of prescriptions were rapidly discontinued within a month before patients could see any clinical benefit. Although there was no information on treatment discontinuation, a few possible reasons that may have contributed to treatment cessation were postulated. Rapid discontinuation of the drug may indicate poor therapeutic efficacy or that these drugs were poorly tolerated by this population. In addition, approximately 29% (n=129; 129/452) of the patients in this study population had been diagnosed with depression. Their feelings of hopelessness and negativity may have contributed to the treatment being prematurely stopped. The preliminary data from a recent conference abstract has shown early discontinuation of orlistat treatment in Scottish young people. Eighty two children aged <19 years (81.7% female), who were newly prescribed orlistat between 2006 and 2009 were identified from the Primary Care Clinical Information Unit (PCCIU) database. Approximately 54% of these children discontinued orlistat within one month of starting treatment and 74% discontinued treatment within 3 months (Sun *et al*., 2011). The authors concluded that discontinuation of orlistat treatment could be a potential signal for ADRs. However, there is no detailed information in the abstract to further explain their conclusion.

At present, there is only one drug (orlistat) approved for obesity treatment in adults in the UK. Several marketed drugs have been considered for the treatment of obesity (Chapter 1, section

1.5). Of these, metformin has been suggested as the best choice of drug for obesity treatment as obese patients are more likely to have metabolic syndromes. A study from the Diabetes Prevention Program has reported that both metformin and lifestyle change reduced the incidence of type 2 DM in adults (Knowleret *et al*., 2002). As obesity in children is a major predictor of developing type 2 DM later in life (Kahn *et al*., 2000; Franks *et al*., 2007), it is expected that in clinical practice metformin will gain in popularity for treating obesity in young people. A drug utilisation study of metformin prescribing in young people was conducted to investigate its prescribing trend and the indications for prescribing it in primary care to children and adolescents in the UK. Increased prescribing of metformin over the past decade was observed in this study, especially in teenage girls aged 16-18 years. Polycystic ovary syndrome (PCOS) was the most common indication for metformin prescribing in girls followed by diabetes. Approximately 7.6% (n=22; 22/290) of the patients received metformin, only for the treatment of obesity between January 2000 and December 2010. As sibutramine was withdrawn in February 2010, more data should be collected in future to determine whether prescribing continues to increase in young people in general practice.

7.1.3.Systematic review and meta-analysis of RCTs of metformin effect on weight loss in non-diabetic children and adolescents

A systematic review and meta-analysis of RCTs was conducted to investigate the efficacy of metformin on obesity treatment in obese non-diabetic children and adolescents. A pooled analysis of 12 RCTs showed that metformin reduced BMI by 0.64 kg/m^2 over 6-months of treatment in this population. There was also an improvement of fasting insulin by 4.15 µU/ml in patients who received metformin treatment. Analyses did not provide strong evidence for a treatment effect on HOMA-IR, cholesterol, HDL, or triglycerides. However the findings of our review must be interpreted with caution, as these studies were short-term and the study populations were small. Currently, there is only one licensed anti-obesity drug for obesity treatment. Metformin has been increasingly used off-label for obesity treatment in recent years. As discussed in Chapter 1.5, several drugs (e.g. diethylpropion, fluoxetine, topiramate) have been recommended as potential anti-obesity drugs in clinical practice. Compared to these, metformin has a good safety profile. However, evidence to support metformin in children and young people remain deficient to date. Large, long-term studies on metformin across different populations are needed in order to establish its role on childhood obesity management.

7.1.4.Drug prescribing for obesity treatment in a regional paediatric weight management clinic

As suggested in the NICE guidelines (2006), treatment with anti-obesity drugs in children and adolescents should be initiated by a specialist in secondary care. However currently there is no published evidence on drug use for obesity management in young people from the secondary care sector in the UK. A large cohort study was conducted at University College London Hospital (UCLH) paediatric weight management clinic between 2007 and 2010. This study represented a cohort of extremely obese young people and was dominated by girls with a White British background. As the individual patient's postcode was captured, we were able to obtain the Indices of Multiple Deprivation (IMD) 2007 score to assess the deprivation in this study population. The majority of patients in this population were living in deprived areas. The percentage of obese patients was almost four times higher in the most deprived decile (decile 1=19%) compared to the least deprived decile (decile 10=5%) in our study. Our finding is similar to the National Child Measurement Programme in Worcestershire. Their report has also shown that the prevalence of obese children in the most deprived decile (IMD decile 1) is double that in the least deprived decile (IMD decile 10) during 2007-2008 and also 2009-2010 (National Child Measurement Programme, 2011). The association of deprivation with childhood obesity has long been recognised. Two studies have demonstrated a strong association between childhood obesity and deprivation in the UK (Kinra *et al*., 2000; Conrad & Capewell, 2012).

In the secondary care study, more patients received a drug together with lifestyle intervention (advice on healthy diet and exercise) for obesity treatment than patients who received only lifestyle intervention. This indicates that the national guideline (NICE 2006) may have had an effect on prescribing practice in secondary care for obesity management in young people. Metformin was the drug most commonly prescribed to obese young people whereas the use of orlistat or sibutramine was low. Although we were unable to obtain data on co-morbidities for this study population, it is believed that the majority of obese patients who received metformin may have metabolic syndromes (Viner & Nicholls, 2005). Although this was a large cohort study from a regional secondary care setting, it is not appropriate to extrapolate these prescribing patters to other specialist care across the UK.

As this study population was relatively large, subsequently we were able to conduct an observational study to determine the effect of metformin treatment in this population. There were significant reductions for BMI SDS in both girls and boys treated with metformin together with lifestyle intervention at 6 months (within group comparison). BMI was only significantly reduced in girls treated with metformin and lifestyle intervention treatment but not in boys (within group comparison). Overall, the reduction of BMI and BMI SDS were not significant (between group differences). When comparing by gender, there was a small but significant effect of metformin and lifestyle intervention treatment on BMI SDS in girls compared to the girls who only received lifestyle intervention only.

7.1.5.Anti-obesity drug prescribing to young people: a national GP questionnaire survey study

In the UK, no study has been conducted specifically to evaluate clinicians' experiences on prescribing drugs to obese young people as treatment. By utilising a primary care, an electronic healthcare database (THIN), we were able to demonstrate clinicians' views towards prescribing drugs to young people for obesity treatment. Furthermore, we were able to demonstrate prescribing attitudes across different healthcare settings (primary care and secondary care). Our findings have shown that more than half of GPs initiating medication did not seek advice from specialists in secondary care. Most GPs reported that metformin was prescribed for the treatment of PCOS (76.1%; 35/46) not for obesity treatment (4.3%; 2/46). This is consistent with our findings using another primary care database (IMS DA) (Chapter 4.3) which showed that majority of metformin prescriptions were issued for PCOS treatment not for obesity treatment. The majority of GPs have low levels of confidence in prescribing drugs to young people compared to adults, especially metformin. Despite comprehensive NICE guidance on childhood obesity management, nearly 90% of GPs supported and suggested a need to develop simple and easy guidance to assist them with prescribing medication to obese children and adolescents. They also suggested that the new guidance should also include guidance on the use of non-pharmacological interventions. Approximately one-quarter of GPs did not know whether their patients had experienced any adverse drug events, and one-third of GPs did not know the treatment outcome. This survey study highlights a need to improve current practice in childhood obesity management in the UK.

7.2.Strengths and Limitations

In this thesis, different epidemiological study designs were applied to investigate anti-obesity drug use in children and adolescents which enable us to demonstrate anti-obesity drug prescribing trends and patterns in both primary care and secondary care as well as the efficacy and ADRs of their use from published RCTs. However, there are methodological issues that need to be addressed.

Systematic reviews and the statistical technique of meta-analysis are important 'tools' to synthesise data from several RCTs to ascertain the efficacy and the commonly reported ADRs for a particular drug used to treat a particular condition. One potentially serious limitation of systematic reviews and meta-analysis is publication bias. Studies that have significant findings are more likely to be published than the studies without significant and/or negative findings (Hopewell *et al*., 2009). A practical solution to deal with publication bias is the "funnel plot". This is a statistical method to detect publication bias in systematic reviews and meta-analysis, by plotting intervention effect estimates from individual studies against the measure of each study's size (Cochrane, 2006). Due to the small number of included RCTs in our meta-analysis, we were unable to assess publication bias in our review using this method. In our review, all studies included for meta-analysis had demonstrated the effectiveness of orlistat and sibutramine on weight loss. Two RCTs were included in the meta-analysis to estimate efficacy and adverse drug reactions of orlistat (Chanoine *et al*., 2005; Maahs *et al*., 2006). The study by Chanoine *et al*. (2005) was industry-funded (Hoffmann-La Roche Ltd). The 4 RCTs of sibutramine included were all industry-funded (Abbott Laboratories Ltd). It appears that these published fully or partly industry-funded RCTs of anti-obesity drugs treatment all reported positive outcomes. In our systematic review and meta-analysis, we found that adverse reactions of orlistat and sibutramine treatment patients experienced from RCT data were tolerated. Although the RCT design is considered the "gold standard" for investigating drug efficacy, some severe ADRs are unlikely to be detected during the trial period due to e.g. short length of follow up, the limited numbers of patients, and exclusion/inclusion criteria for patients. In addition, ADRs may have been under-reported in the clinical trials. A review study which investigated 192 published pharmaceutical trials, found that less than one third of the trials had adequate reporting of the ADRs or laboratory toxicological findings (Rothwell, 2005). Therefore, we cannot completely rule out publication bias in our review. Furthermore, we unexpectedly observed a rapid discontinuation of anti-obesity drug treatment in our population-based study. This early discontinuation of treatment may indicate poor efficacy of the treatment or intolerance to the ADRs.

An issue that also needs to be addressed is the validity of assessing the effect of drug treatment in observational studies. This has long been debated and remains controversial (McKee *et al*., 1999; Concato *et al*., 2000). Despite this, observational studies are an important study design for determining the effectiveness of drug treatment in routine clinical practice (Faries *et al*., 2007; Nallamothu *et al*., 2008), as RCTs can only provide evidence of treatment effect under controlled conditions in a selected group of patients, for a defined period of treatment (Klungel *et al*., 2004). Stratification may be carried out in observational studies to divide patients into subgroups or strata on the basis of characteristics that are potentially confounding factors the analysis (Lu, 2009). It is suggested that sufficient baseline information should be collected to overcome any confounding by pre-existing differences, when comparing treated and untreated groups in an observational study (Jepsen *et al*., 2004; Stürmer *et al*., 2007). Due to the absence of information on co-morbidities and co-prescribing medication (potential confounding factors), in our study, the estimated metformin treatment effect may be biased by differences in baseline risk for other factors and/or other treatment interventions (e.g. psychological intervention). In recent years, several methods have been proposed to overcome the criticisms of assessing treatment effects in observational studies. The main objective of these methods is to overcome the potential bias and selection bias caused by the non-randomised assignment of treatment (Klungel *et al*., 2004). Table 7.1 summarises the strengths and limitations of the epidemiological study designs used in this thesis to investigate the drug treatment effect (Hannan, 2008; Nallamothu *et al*., 2008). A systematic review and meta-analysis is a systematic and quantitative approach to synthesise existing data to answer important therapeutic questions. This method has been widely used to assess drug treatment and identify commonly occurring ADRs by combining evidence from diverse study designs and study populations from published RCTs. The meta-analysis is a powerful statistical method in which studies can be weighted according to their sample size and provides an overall estimate of the treatment effect. However, the main limitations of systematic reviews and meta-analyses are publication bias and flaws in the included studies (Sutton *et al*., 2000). If systematic reviews and meta-analyses are done and interpreted carefully this type of study is extremely helpful in assessing the effect of drug treatment and identifying frequently occurring ADRs.

As discussed, due to the absence of randomisation procedure in observational studies, this type of study design is always limited by confounding or selection bias for determining drug treatment effect (Nallamothu *et al*., 2008). In contrast, the randomisation procedure conducted in a RCT design ensures that certain kinds of potential selection bias (e.g. inclusion and exclusion criteria) will be removed, such as clinician preference for giving certain treatment to selected patients and also that unobserved differences in patient characteristics are randomly distributed between treatment groups (Klungel *et al*., 2004). Several statistical approaches have been implemented to overcome the absence of randomisation in observational study for assessing therapeutic effect such as asymmetric stratification, propensity score adjustment, and multivariate confounder scores (Klungel *et al*., 2004). With appropriate statistical techniques, an observational study is an invaluable source for informing clinical practice.

Table 7.1: Strengths and limitations of study designs used to investigate drug treatment effect in this thesis (adapted from Hannan, 2008; Silverman, 2009)

Study design	Strengths	Limitations
Systematic review and Meta-analysis	1.Systematic review can provide helpful information in clinical decision making 2. Pooling of data allows for evaluations of small but important subgroups of patients 3. Provides insights into heterogeneity of treatment effects across studies 4. Systematically assess concurrent ADRs for specific drugs 5. Studies can be weighted according to their sample size 6. Meta-analysis can save considerable time and resources between a research finding and the clinical implementation of a new therapy, by accumulating evidence as it becomes available	1.Susceptible to study design limitations within individual studies 2.Suffers from potential publication and reporting bias of large treatment effects 3.Heterogeneity may be inadequately addressed in study selection or analysis 4.Difficult to obtain patient-level data from investigators 5. ADRs data can only be obtained from published results.
Observational study	1.Involves a large and diverse population of patients in treated in 'real world' clinical practice 2. It can investigate multiple outcomes 3. It can provide insight into the clinical context in which multiple therapies are delivered 4. It can be relatively inexpensive and can be performed relatively rapidly 5. Results can be generalized to general population	1.If conducted prospectively, it may take years to complete 2. Confounding or selection bias of patients-or the two combined-make it difficult to compare treated and untreated patients 3. Several statistical approaches are available to investigate treatment effect but may be inconsistently applied or reported

Abbreviation: ADR, adverse drug reaction; RCT, randomised controlled trial.

7.3.Areas for recommended future research

This thesis examined the efficacy and safety of anti-obesity drugs from RCTs, and also the prescribing patterns of these drugs in both primary and secondary care settings, in the UK. Below are suggestions for future research.

The first area of future research identified from the drug utilisation studies would be to investigate the reasons for discontinuation of anti-obesity drug treatment and what approaches could be used by young people to lose weight after drug treatment failure. In this thesis, it was not possible to investigate the reasons for the rapid discontinuation of the drug therapy, due to the limited coded information available from the primary care database. Qualitative research is needed to examine the reasons and possible factors affecting the cessation of anti-obesity drug treatment. Qualitative research is currently carried out by other team members of PROMSE programme. A GP questionnaire study could be conducted to investigate whether anti-obesity drugs are being prescribed in accordance with the 2006 NICE guideline on obesity management. Also, an interview study could be carried out to investigate reasons for anti-obesity drug discontinuation and the experience of these drugs used in children and adolescents.

A second area of future research would be to investigate to what extent other factors affected the treatment outcomes in the observational cohort study conducted at the UCLH paediatric weight management clinic. Additional information such as psychological interventions, co-morbidities, and co-prescribing medications, anthropometric (e.g. fasting glucose, insulin, fasting glucose) and lipid (e.g. high-density lipoprotein cholesterol) levels could be obtained from other sources. This additional information could be used to identify potential factors that may affect treatment outcome.

The third area of further research should be to develop a collaborative, prospective, obesity management surveillance network for children and adolescents across other specialist centres in the UK. This could examine drug prescribing patterns along with other interventions (e.g. psychological intervention, bariatric surgery) for weight management, and it could also monitor the clinical effectiveness and any complications of different interventions in a much larger population. As the findings on drug prescribing patterns for obesity treatment reported in this thesis came from only one specialist centre and they cannot be generalised to other specialist centres across the UK.

The fourth area of further work would be to investigate drug prescribing trends (orlistat and metformin) over the same period of time in both primary care and secondary care. This could provide us with a clear picture of whether metformin use for obesity treatment in young people continues to increase in clinical practice.

The final area of work identified for further research is the long-term efficacy and safety of metformin for weight loss. To date, the long-term (over 1 year) efficacy and identification of adverse drug reactions after long term treatment with metformin in obese young people remains unknown. There are a few on-going RCTs investigating efficacy of metformin for obesity treatment in adults. However, it is not appropriate to extrapolate adult data to children and adolescents due to different physiological responses. A large-scale long-term RCT to investigate metformin efficacy and safety in young people is needed. Although a RCT is a gold standard to investigate therapeutic effect, this type of study design can sometimes add complexity with regard to cost and time. Also, the RCT study is normally limited to a selected targeted population so it is difficult to generalise to routine clinical practice. With appropriate statistical techniques applied, an observational study should also be considered, as it can assess the effect of metformin treatment at a population level. Propensity score matching is a relatively new statistical method, which has been extensively used in observational studies to determine treatment effects. Using a primary care database and a propensity score matching technique, the effect of metformin treatment on weight loss in a real-life clinical practice, could be investigated. Furthermore, this study design could minimise the cost and time compared to a RCT.

7.4.Conclusions

The findings from this thesis advanced our understanding of the efficacy, effectiveness, safety and prescribing patterns of anti-obesity drug treatments in children and adolescents in different clinical settings. The efficacy of anti-obesity drugs from published short-term RCTs (6 months) has shown that both orlistat and sibutramine together with behavioural support reduced BMI in children and adolescents but a high frequency of gastrointestinal adverse reactions was reported amongst those patients who received orlistat. Patients who received sibutramine were reported to have higher systolic and diastolic blood pressure and heart rate compared with those treated with placebo. In primary care, the prescribing of anti-obesity drugs (orlistat, sibutramine) to young people aged 0-18 years increased between 1999 and 2006 but a high proportion discontinued drug treatment within a month. This may indicate that these drugs were poorly tolerated or not effective.

As the limited drug of choice, metformin has been recommended for obesity treatment. There was a steady increase in metformin prescribing in particular to teenage girls aged 16-18 years between 2000 and 2010, in primary care; the main indication for it being prescribed was PCOS. Our updated meta-analysis of 12 RCTs showed a small effect of metformin on BMI reduction over 6 months of treatment in obese young people without diabetes. Frequently reported adverse events were gastrointestinal problems and no serious ADR was reported in any of these trials. At a specialist care weight management clinic more patients received metformin for obesity treatment between 2007 and 2010 than received orlistat or sibutramine. Metformin treatment together with lifestyle intervention produced a small but statistically significant reduction of BMI SDS compared to lifestyle intervention alone in girls after 6 months of treatment.

Despite clear NICE guidance that recommended anti-obesity drugs should be started in a specialist paediatric setting before they can be continued in primary care (2006), our questionnaire survey study suggested that over half of GPs did not receive specialists' advice before they initiated medication (orlistat or metformin) treatment to obese young people. Also, GPs expressed a need to develop a simple and easy to follow guidance for pharmacological intervention as well as for non-pharmacological interventions. Most GPs does not know the treatment outcome and whether their patient had had an adverse drug event of the drug their patients were taking for obesity treatment. In addition, some GPs have expressed lower level of confidence to prescribing drug to children compared to adults. There is an urgent need to improve childhood obesity management in the UK practices.

To date, research on the long-term efficacy of metformin as a treatment for obesity is required, as currently it is not licensed for obesity treatment in either children or adults nor has it been recommended as a pharmacological treatment in the current NICE guidance on obesity management in adults and children. As there is increased use of metformin for obesity treatment, in both primary and secondary care, clinicians should use the most up-to-date evidence when prescribing metformin for obesity treatment in young people. The findings from this thesis have increased our knowledge of anti-obesity drug use in both primary and secondary care, for children and adolescents. This knowledge should enable clinicians and healthcare providers to offer more effective pharmacological interventions for obesity management in young people in clinical practice, as drug treatment has been an important adjunct to lifestyle intervention for obesity management in young people.

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Appendices

Appendix 1: MEDLINE (through PubMed) search strategy for randomised controlled trials of anti-obesity drugs

Searched date from January 1996 to January 2008	
Step	Search terms
1	orlistat [Title/abstract]
2	xenical [Title/abstract]
3	sibutramine [Title/abstract]
4	reductil [Title/abstract]
5	rimonabant [Title/abstract]
6	acomplia [Title/abstract]
7	or/#1-#6
8	obes* [Title/abstract]
9	obesity[MeSH Terms]
10	weight gain* [Title/abstract]
11	weight gain [MeSH terms]
12	weight loss [MeSH terms]
13	body mass index [MeSH terms]
14	adipos* [Title/abstract]
15	overweight [Title/abstract]
16	over weight [Title/abstract]
17	binge eating disorder* [Title/abstract]
18	fat overload syndrome*[Title/abstract]
19	overeat* [Title/abstract]
20	overfeed* [Title/abstract]
21	over eat* [Title/abstract]
22	over feed* [Title/abstract]
23	weight loss* [Title/abstract]
24	weight cycling [Title/abstract]
25	weight reduce* [Title/abstract]
26	weight losing [Title/abstract]

27	weight maint* [Title/abstract]
28	weight decreas* [Title/abstract]
29	weight watch* [Title/abstract]
30	weight control* [Title/abstract]
31	or/#8-#30
32	randomized controlled trial [Publication type]
33	randomized controlled trials [MeSH terms]
34	random allocation [MeSH terms]
35	random* [Title/abstract]
36	alloc* [Title/abstract]
37	assign* [Title/abstract]
38	controlled clinical trial [Publication type]
39	clinical trial [Publication type]
40	clinical trials [MeSH terms]
41	clinical trial* [Title/abstract]
42	cross over studies [MeSH terms]
43	cross over stud* [Title/abstract]
44	crossover stud* [Title/abstract]
45	cross over trial* [Title/abstract]
46	crossover trial* [Title/abstract]
47	cross over design* [Title/abstract]
48	crossover design* [Title/abstract]
49	double blind method [MeSH terms]
50	single blind method [MeSH terms]
51	singl* blind* [Title/abstract]
52	singl* mask* [Title/abstract]
53	double* blind* [Title/abstract]
54	double* mask* [Title/abstract]
55	trebl* blind* [Title/abstract]
56	trebl* mask* [Title/abstract]
57	tripl* blind* [Title/abstract]

58	tripl* mask* [Title/abstract]
59	placebo [MeSH terms]
60	placebo* [Title/abstract]
61	research design [MeSH terms]
62	evaluation studies [MeSH terms]
63	follow up studies [MeSH terms]
64	prospective studies [MeSH terms]
65	prospective* [MeSH Terms]
67	prospective* [Title/abstract]
68	or/#32-#67
69	child* [Title/abstract]
70	children [Title/abstract]
71	child [MeSH terms]
72	paediatr* [Title/abstract]
73	pediatr* [Title/abstract]
74	pediatrics [MeSH terms]
75	adolescent [Title/abstract]
76	adolescent [MeSH terms]
77	or/#69-#76
78	#7 AND #31 AND #68 AND #77

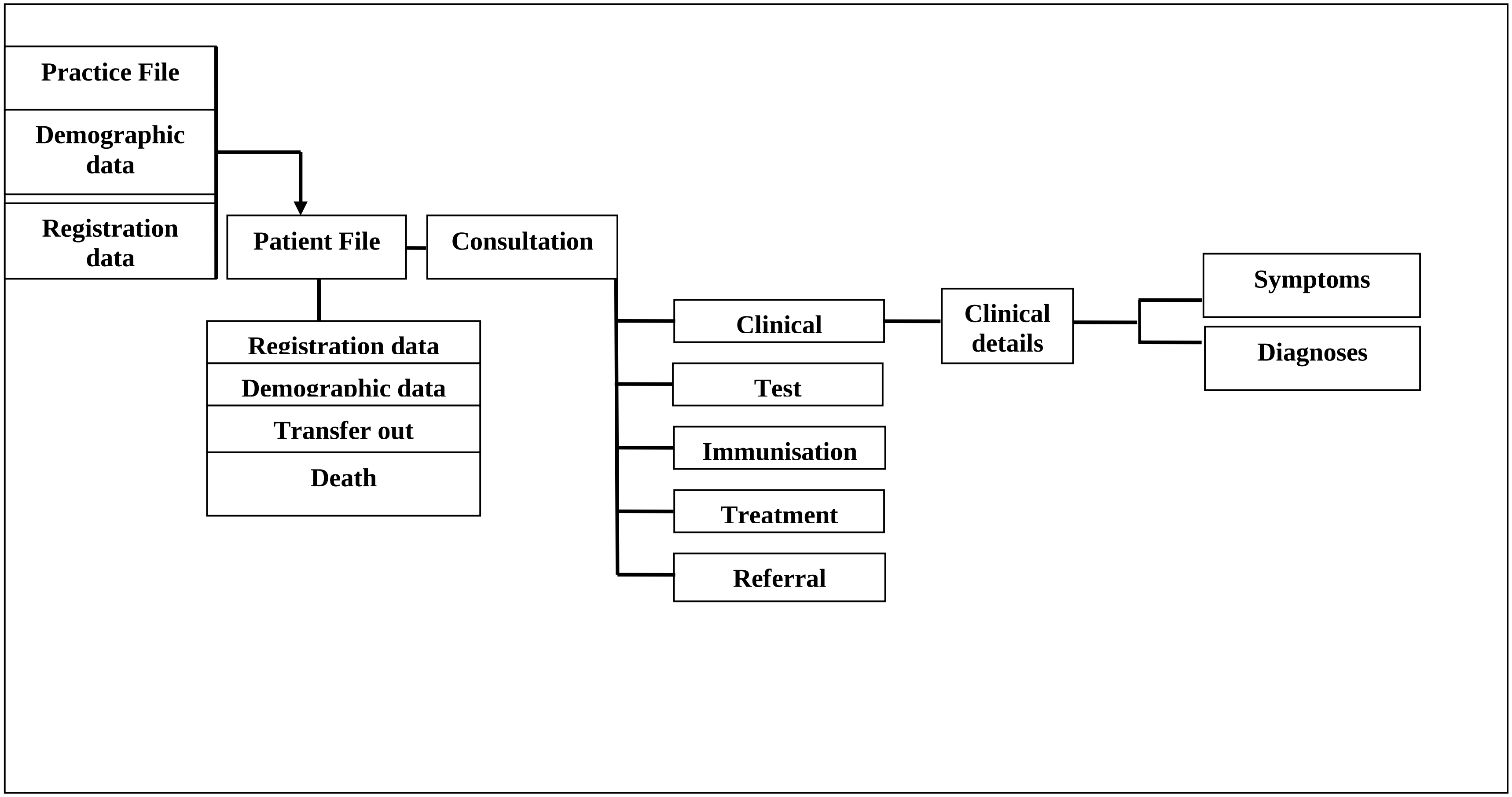
Appendix 2: EMBASE search strategy for randomised controlled trials in anti-obesity drugs

Searched Date from January 1996 to January 2008	
Step	Search terms
1	body weight/ or weight gain/ or weight reduction/ or birth weight/
2	obesity
3	or/ #1-#2
4	antiobesity agent
5	sibutramine
6	orlistat
7	xenical
8	reductil
9	rimonabant
10	acomplia
11	or/ #4-#10
12	3 AND 11
13	randomised controlled trial
14	meta analysis
15	clinical trial
16	double blind
17	double dummy
18	random
19	or/#13-#18
20	12 AND 19
21	child or adolescent
22	20 AND 21

Appendix 3: CENTRAL (on the Cochrane Library) search strategy for randomised controlled trials in anti-obesity drugs

Searched Date from January 1996 to January 2008	
Step	Search terms
1	body weight/ or weight gain/ or weight reduction/ or birth weight/
2	obesity
3	or/ #1-#2
4	antiobesity agent
5	sibutramine
6	orlistat
7	xenical
8	reductil
9	rimonabant
10	acomplia
11	or/ #4-#10
12	3 AND 11
13	randomised controlled trial
14	meta analysis
15	clinical trial
16	double blind
17	or/#13-#16
18	12 AND 17
19	child or adolescent
20	18 AND 19

Appendix 4: Schematic diagram to illustrate the relational linking of data files in FF-GPRD



Appendix 5: Business Objectives Report for retrieving records from FF-GPRD for anti-obesity drugs

Business Objects report **File name/location:** R:\userdocs\antiobesity_patients.rep

Date created: 11/09/2007

Objects

Practice EID (Current), Patient EID (Current), Birth Year (Current), Birth Month (Current), Current Gender (Current), GPRD Product Code (Event), Age at event, Event date*

Conditions

EventType = 'Therapy'

AND Age at Event Year < 19

AND (GPRD Product Code (Events) in list (given below)

AND Event date *Between 01/01/1992 and 31/08/2007

AND Patient Record Deleted Flag Equal to "N"

AND Standard Patient Criteria

AND Event Deleted Flag = 'N'

GPRD Product Codes
4070960, 4084882, 4095773, M02501001, M02501002, M10585001

Appendix 6: Anti-obesity drug prescribing in children and adolescents study protocol for GPRD

ISAC APPLICATION FORM:
PROTOCOLS FOR RESEARCH USING THE GPRD DATA

ISAC use only: Protocol Number Date submitted		**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** **ISAC**@gprd.com

1. Study Title
Anti-obesity drugs prescribing in children and adolescents

2. Does this protocol describe a purely observational study using GPRD data (this may include the review of anonymised free text or access to anonymised data via the GPRD data linkage scheme)?

Yes ☒ No ☐

3. Does this protocol involve requesting any additional information from GPs?

Yes ☐ No ☒

If yes, please indicate what will be required:

Completion of questionnaires by the GP*	Yes ☐	No ☐
Provision of anonymised records (e.g. hospital discharge summaries)	Yes ☐	No ☐
Other (please describe)		

*any questionnaire for completion by GPs needs to be approved by ISAC before being sent out for completion.

GUIDANCE ON ANSWERING QUESTIONS 4-6:
These questions must be completed by all applicants. You should note the following:

(i) if you have answered NO to question 2, you will have to seek separate ethics approval from an NHS Research Ethics Committee for this study

(ii) if you have answered YES answered to question 2 above and you will be using data obtained from the GPRD Group at the MHRA, this study does not require separate ethics approval from an NHS Research Ethics Committee.
If you will be using data obtained from EPIC, you will need to consult the data provider regarding their arrangements for obtaining ethics approval for the study.
NB: Answering YES to question 2 means that the answers to questions 4-6 should all be NO. If any of the answers below are YES please review your answer to question 2 as it should be NO.

4. Does the study involve linking to patient *identifiable* data from other sources? Yes ☐ No ☒

5. Does this study require contact with patients in order for them to complete a questionnaire? Yes ☐ No ☒

6. Does this study require contact with patients in order to collect a sample? Yes ☐ No ☒
If yes, please state what will be collected

7. Type of Study *(please tick one box below)*

Adverse Drug Reaction	☐	Drug Use	☒	Disease Epidemiology	☐
Pharmacoeconomic	☐	Drug Effectiveness	☐	Other	☐

8. Data source *(please tick one box below)*

GPRD Division at MHRA		Other *(please specify)*	☐
Full Feature on-line access	☒		

Ad hoc dataset	☐
MRC dataset	☐
Other commissioned study	☐

9. Financial Sponsor of study

MRC* ☐ Pharmaceutical Industry *(please specify)* ☐

Government / NHS *(please specify)* ☐ Other *(please specify)* ☒ European Commission via the Taskforce European Drug Development for the Young (TEDDY) network of Excellence European Commission Framework 6 Programme 2005-2010.

None ☐

* Tick this box if you wish to access GPRD data under the MRC licence with GPRD. It is expected that if you use the MRC licence, no other direct commercial/public sector funding for this study will be sought/has been applied for or is in place. If funding is in place, but does not cover the use or extraction of GPRD data, please tick the boxes for relevant funding sources (including MRC) and provide details in the protocol of why funding under the MRC licence is required.

10. Is the study intended for

Publication in peer reviewed journals ☒ Presentation at scientific conference ☒

Presentation at company/institutional meetings ☒ Other

11. Principal Investigator (full name, job title, organisation & e-mail address for correspondence regarding this protocol)

Professor Ian Wong, DH National Public Health Career Scientist & Professor of Paediatric Medicines Research, Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London. E-mail: ian.wong@pharmacy.ac.uk

12. Affiliation (full address)

Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX

13. Type of Institution *(please tick one box below)*

Academia	☒	Research Service Provider	☐	Pharmaceutical Industry	☐
NHS	☐	Government Departments	☐	Others	☐

14. Experience/expertise available

Please complete the following questions to indicate the experience/expertise available within the team of researchers actively involved in the proposed research, including analysis of data and interpretation of results

	Previous GPRD Studies	Publications using GPRD data
None	☐	☐
1-3	☐	☒
> 3	☒	☐

	Yes	No
Is statistical expertise available within the research team?	☒	☐
If yes, please outline level of experience		
Is experience of handling large data sets (>1 million records) available within the research team?	☒	☐
If yes, please outline level of experience		
Is UK primary care experience available within the research team?	☒	☐

If yes, please outline level of experience

15. Other collaborators (if applicable: *please list names and affiliations of all collaborators*) Dr. Russell Viner-Adolescent Medicine UCL Institute of Child Health & Honorary consultant in Adolescent Medicine & Endocrinology UCL Hospitals & Gt. Ormond St. Hospital London. Dr. Antje Neubert- Centre for Paediatric Pharmacy Research Miss Yingfen Hsia- Centre for Paediatric Pharmacy Research

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using GPRD data. These instructions are available on the GPRD website (www.gprd.com/ISAC). All protocols using GPRD data which are submitted for review by ISAC must contain information on the areas detailed in the instructions. IF you do not feel that a specific area required by ISAC is relevant for your protocol, you will need to justify this decision to ISAC.
Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.
Please note, your protocol will be returned to you if you do not complete this checklist, or if you answer 'no' and fail to include justification for the omission of any required area.

	Included in protocol?		
Required area	**Yes**	**No**	**If no, reason for omission**
Objective, specific aims and rationale	☒	☐	
Background	☒	☐	
Study design	☒	☐	
Study population, including estimate of expected number of relevant patients in the GPRD	☒	☐	
Sample size/ power calculation	☐	☒	**This is a cohort study. The sample size in the GPRD paediatric population is large enough to investigate prevalence and incidence of overweight/obesity and prescribing patterns.**
Selection of comparison group(s) or controls	☐	☒	**The study is not a case-control or comparative cohort study.**
Exposures, outcomes and covariates	☒	☐	
Data Analysis	☒	☐	
Patient/ user group involvement †	☐	☒	**This study does not have involvement of patients or user groups.**
Limitations of the study design, data sources and analytic methods	☒	☐	
Plans for disseminating and communicating study results	☒	☐	

† It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement, and/or in the interpretation of the results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Please indicate whether or not you intend to engage patients in any of the ways mentioned above.

ISAC strongly recommends that researchers using GPRD consider registering as a NRR data provider in order that others engaged in research within the UK can be made aware of current works. The ***National Research Register (NRR)*** *is a register of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service. Information on the NRR is available on www.nrr.nhs.uk .*

Study title: obesity and overweight in children and adolescents

Aim

To investigate the prevalence of obesity, overweight in children and adolescents aged 0-18, and to estimate prevalence and incidence rate of anti-obesity treatment.

Objectives

- To identify patients who were overweight and obesity in the GPRD paediatric population (0-18 years).
- To estimate the prevalence and incidence of anti-obesity drugs prescribing in this study population.

Background

Obesity in childhood has caused global concern in recent years. Evidence has shown a continued increase of obesity and overweight in youths. The US study (the National Health and Nutrition Examination Survey) reported that 10% of children aged 2-5 was overweight and 15% amongst children aged 6-19 in 1999-2000 [1]. Similarly, studies from continental Europe have shown an increased prevalence of obesity and overweight in children and adolescents [2-4].

In the UK, data from the Health Survey for England (HSE) reported the prevalence of overweight and obesity increased from 22.7% in 1995 to 27.7% in 2003 amongst children aged 2-10 [5]. Previous national studies also demonstrated an increased prevalence of obesity and overweight in children [6-9]. Although theses studied had been carried out to investigate obesity and overweight in youths, it should be addressed that data from most studies were collected during the mid 1990s which can not reflect the current situation. Also, these studies did not examine anti-obesity drugs prescribing patterns.

Obesity in children and adolescents is a serious public health as this condition can persist into adulthood. Consequently, it will lead to several complications such as diabetes, cardiovascular diseases [10]. Information on obesity prevalence and anti-obesity drug prescribing in paediatric population are particularly important as this is directly related to health care plans and management. Therefore, we would like to propose to investigate the prevalence, incidence of obesity, overweight and anti-obesity prescribing pattern in children and adolescents using the General Practice Research Database (GPRD).

1. Ogden CL, Flegal KM, Carroll MD, and Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. JAMA 2002, 288: 1728-1732.
2. Kautiainen S, Rimpela A, Vikat A, and Virtanen SM. Secular trends in overweight and obesity among Finnish adolescents in 1977-1999. International Journal of Obesity 2002, 26: 544-552.
3. Schober E, Rami B, Kirchengast S, Waldhor T and Sefranek R. Recent trend in overweight and obesity in male adolescents in Austria: a population-based study. European Journal of Pediatrics 2007, 166: 709-714.
4. Papadimitrious A, Kounadi D, Konstantinidou M, Xepapadaki P, and Nicolaidou P. Prevalence of Obesity in elementary schoolchildren living in northeast Attica, Greece. Obesity 2006, 14: 1113-1117.
5. Jotangia D, Moody A, Stamatakis E, and Wardle H. Obesity among children under 11. Department of Health. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4109245 [accessed on 06/09/2007].
6. Reilly JJ, and Dorosty AR. Epidemic of obesity in UK children. Lancet 1999, 354: 1874-1875.
7. Chinn S, and Rona RJ. Prevalence and trends in overweight and obesity in three cross sectional studies of British children, 1979-1994. British Medical Journal 2001, 322: 24-26.
8. Kinra S, Nelder RP, and Lewendon GJ. Deprivation and childhood obesity: a cross sectional study of 20973 children in Plymouth, United Kingdom. Journal of Epidemiology and Community Health 2000; 54: 456-460.

9. Jebb SA, Rennie KL, Cole TJ. Prevalence of overweight and obesity among young people in Great Britain. Public Health Nutrition 2003, 7: 461-465.
10. Freedman DS, Dietz WH, Srinivasan SR, and Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. Pediatrics 1999, 103: 1175-1182.
11. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Archives of Disease in Childhood 1995, 73: 25-29.

Study Design
Descriptive cohort study
Study Population
The study population will comprise all patients in GPRD who are:

- 18 years or younger
- Have at least 1 year up-to-standard data available, except children < 1 year-old.
- Have a known gender.
- Have an acceptable patient registration status (permanent, transferred out)

Inclusion Criteria for cases
Patients aged 0-18 years between 1 January 1992 to 31 August 2007 who had a diagnosis of obesity and/or obesity-related complications (Annex 1) and/or received at least one prescription for anti-obesity drug(s) (Annex 2).
Definition of obesity and overweight for cases
The value of BMI (Body Mass Index) will be used as a mean to define overweight and obese. Overweight is defined as BMI above the 85th percentile. Obesity is defined as BMI ≥95th percentile [11].
Diagnosis and Exposure of Interest
Obesity and obesity-related complications diagnosis
Anti-obesity drugs
Body mass index (BMI)
Selection of Controls
None
Clinical Outcome of Interest
This is a descriptive epidemiological study; therefore there are no specific clinical outcomes of interest. However, medical codes and clinical events such as body mass index (BMI) will be examined for diagnosis of obesity, overweight and prescription of anti-obesity drugs.
Data Collection
Data will be extracted using standard GPRD data tools. Stata/SE version 9.1 (StataCorp, College Station, Texas, United States) will be used for data management and statistical analysis.
Outcome
Cases will be identified from the cohort described above. Patients in the cohort will be followed from the date of entry into the database. Cases will be defined as patients who received prescriptions for anti-obesity drug, and/or a medical code related to obesity.
Data analysis
Prevalence will be defined as the number of patients with a record of obesity, overweight, obesity-related complications and/or prescription of anti-obesity drug during each year of investigation. The calculation for prevalence is given below:

$$\text{Prevalence} = \frac{\text{Number of patients with a diagnosis of obesity or prescription of anti-obesity drug x 1000}}{\text{Total number of patient in GPRD population aged 18 years and younger}}$$

Prevalence will be presented as number of patients per 1000 for each year of the study.

Incidence cases will be defined as patients who had no record of obesity, overweight, obesity-related complications and/or prescription of anti-obesity drugs in the previous year but thereafter. Patients who received their first prescription of anti-obesity drug and/or first obesity medical code under 1 year-old, they will also be considered as incident cases. The incidence will be calculated as the number of new cases divided by the person years at risk in the GPRD paediatric population (aged 0-18 years).The calculation for incidence is given below:

$$\text{Incidence} = \frac{\text{Number of patients with a diagnosis of obesity or prescription of anti-obesity drug x 1000}}{\text{Total number of patient years in GPRD population aged 18 years and younger}}$$

Incidence will be presented as number of patients per 1000 patient years for each year of the study.

The prevalence and incidence will be presented with 95% confidence intervals and stratified by age, gender, type of drug, and year of study. A χ^2 test (Cochran-Armitage test for trend) will be used to examine the yearly trend in anti-obesity drug prescribing. Boy-girl prevalence ratio for anti-obesity prescribing will be calculated using the Taylor series method with 95% confidence intervals.

Limitations

The GPRD does not provide data on dispensing of medication or patients' compliance. The absense of dispensing and compliance data is an acknowledged limitation of automated databases. The GPRD does not contain ethnicity information, so it is not possible to investage whether this factor is associated with obesity and overweight.

Methods of disseminating the research

Results of the study will be presented in conferences and submitted to scientific journals.

Appendix 7: GPRD ethics approval letter for obesity study

Appendix 8: Study protocol for IMS DA

Confidential - not for publication | No: 2010/ISEAC/001

INDEPENDENT SCIENTIFIC AND ETHICAL ADVISORY COMMITTEE

APPLICATION FOR APPROVAL FOR INVESTIGATION INVOLVING THE UK DISEASE ANALYZER DATABASE

1. BRIEF TITLE OF PROJECT

Drug utilisation study in paediatric patients in 1992-2010

2. PRINCIPAL RESEARCHERS

(Include qualifications, position and role in study)

Name	Post
Prof Ian Chi Kei Wong	Director
Dr Macey Murray	Teaching and Research Fellow
Ms Yingfen Hsia	Research Fellow

Official Address

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3. SPONSOR OF STUDY

(If any - please state any commercial or financial interests)

Centre for Paediatric Pharmacy Research, University of London.
No other commercial or financial interests.

4. ABSTRACT OF THE PROPOSED STUDY

Briefly describe the study and what you intend to determine from the data available on the Disease Analyzer - Mediplus Database. The scientific case, and the potential importance and implications of any findings and conclusions should be summarised here.

The main objective of this project is to promote research on the safe and effective use of medicines for children, and to expand and integrate knowledge of, and to build research capacity in drug development for male and female children. To achieve these goals, one of the activities is to conduct drug utilisation studies in children whilst using existing clinical databases from different European countries. Data from IMS Disease Analyzer (IMS DA) will be analysed to describe prescribing patterns, prevalence, and incidence of conditions in UK primary care. The results will equip us to identify priorities for further research in the area of medicines for children within Europe.

5. AIMS AND OBJECTIVES OF THE STUDY

Indicate what questions are to be answered from the study and what information you hope to obtain (approximately 250 words)

This drug utilisation study aims to investigate the prescribing patterns, to young people aged 0-18 years, in UK primary care, based on the Anatomical Therapeutic Chemical (ATC) Classification System with respect to number of prescriptions, prevalence, incidence, indication, formulation and dosage, consultations, and specialist referrals. The study period will be between 1 January 1992 and 31 December 2010. Data will be compared with other European countries, e.g. The Netherlands, Italy and the results will be used to prioritise further research in paediatric medicine.

6. SCIENTIFIC BACKGROUND TO STUDY

Complete this section in approximately 250 words including any references to previous work.

Pharmacoepidemiological and prospective cohort studies could provide vital safety and efficacy data on paediatric medicines; however, resources need to be invested into methodological research.[1] Recently, the Department of Health Standing Medical Advisory Committee in England recommended that children's medication prescribing data should be collected for evaluation.[2] Moreover, the need for drug utilisation studies and pharmacovigilance systems for children was specifically proposed in the draft regulations on medicinal products for paediatric use.[3] Undoubtedly, research capabilities using clinical databases will have to be further developed in order to support the rapidly expanding agenda of paediatric medication research.

Several publications have been published used IMS DA database to investigate medication use in paediatric population. [4-10] We consider IMS DA to be a valuable resource for pharmacoepidemiological research, and it provides us with a unique opportunity to study the use of drugs prescribed to children. We believe that so far this database has been underused for paediatric drug research and therefore, this proposed study could further demonstrate the value of IMS DA databases in this area of research.

References:

1. Wong ICK, Sweis D, Cope J, Florence A. Children Medicines Research in the UK – How to move forward? Drug Safety 2003;26(11):529-37.
2. Standing Medical Advisory Committee Advice. Licensing and Prescribing of Drugs in Children (SMAC Advice 5/2001). http://www.advisorybodies.doh.gov.uk/smacdrugschildren.htm (accessed 10/06/2004).
3. Commission Consultation on a Draft Proposal for a European Parliament and Council Regulation (EC) on Medicinal Products for Paediatric Use. Brussels: European Commission 2004.
4. Wong IC, Murray ML, Camilleri-Novak D, Stephens P. Increased prescribing trends of paediatric psychotropic medications. Archives of Disease in Childhood 2004;89(12):1131-2.
5. Murray ML, Thompson M, Santosh PJ, Wong IC. Effects of the Committee on Safety of Medicines advice on antidepressant prescribing to children and adolescents in the UK. Drug Safety 2005;28(12):1151-7.
6. Hsia Y, Neubert A.C., Rani F, Viner RM, Hindmarsh PC, Wong ICK, An increase in the prevalence of type 1 and 2 diabetes in children and adolescents: results from prescription data from a UK general practice database. British Journal of Clinical Pharmacology. 2009: 67(2): 242-249.
7. Hsia Y, Neubert A, Sturkenboom M, Verhamme KMC, Sen EF, Giaquinto C.,Ceci A., Murray ML., Wong ICK on behalf of the TEDDY Network of Excellence. Antiepileptic drug prescribing comparison in three European countries. Epilepsia. 2010;51(5):789-96.
8. Antje Neubert, Katia Verhamme, Macey Murray, Gino Picelli, Y Hsia, Fatma Sen, Carlo Giaquinto, Adriana Ceci, Miriam Sturkenboom, and Ian Wong. The prescribing of analgesics and non-steroidal anti-inflammatory drugs in paediatric primary care in the UK, Italy and the Netherlands. Pharmacol Res. 2010;62(3):243-8.
9. Neubert A, Hsia Y, TW de Jong-van den Berg L, Janhsen K, Glaeske G, Furu K, Kieler H, Nørgaard M, Clavenna A, Wong ICK. Comparison of anti-diabetic drug prescribing in children and adolescents in seven European countries. British Journal of Clinical Pharmacology 2011 (in press).
10. Hsia Y, Dawoud D, Sutcliffe AG, Viner R, Kinra S, Wong ICK. Unlicensed use of metformin in children and adolescents in UK. British Journal of Clinical Pharmacology. 2011 (in press)

7. <u>OUTCOME MEASURES</u>

Indicate the specific primary end point(s) and any secondary end points of the study.

This is descriptive study and therefore there is no end point measure as such. However, we will analyse the data on the following parameters:

1. age and gender of patients
2. prescriptions by ATC High-level (see Annex 1), ATC Therapeutic-level (see Annex 2) and ATC Chemical (molecule)-level.
3. prevalence by calendar year, age & gender
4. formulation and dosages by age
5. indication for which the drugs have been prescribed by age
6. incidence and duration of treatment
7. clinical problems and diagnoses related to treatment

8. consultations and specialist referrals

8 DESIGN

a) STUDY TYPE

E.g. cohort study, case-control study, secular trends in prescribing.

Retrospective cohort study of young people aged 0-18 years, investigating trends in prescribing and drug utilisation.

b) NUMBERS NEEDED

Cases, controls, number of years over which data are needed etc. Assumptions regarding indications of significance level and power likely to be achieved. Please note that IMS can provide top line numbers for potential patients to be included if necessary. All applications should include statistical justification for the numbers to required in a study. This should demonstrate that the results are likely to be interpretable with reasonable confidence. This requirement applies to "descriptive" studies as well as to those involving comparisons of any sort.

This is a descriptive and quantitative study and all patients aged between 0-18 will be included during the study period. The study period will between 1 January 1992 and 31 December 2010. For time-trend analysis, this entire period is possible to detect any significant prescribing change.

c) ELIGIBILITY

Indicate the criteria for both inclusion in, and exclusion from, the study.

Inclusion Criteria

Patients must:

- be aged between 0 and 18 years
- have at least 6 months of data available unless newborn. Newborns will be included in the study cohort regardless of the amount of data available.
- have a known gender

Exclusion Criteria

Patients must:

- not be temporarily registered to their general practice

d) DATA ITEMS TO BE COLLECTED

Data to be used for stratification, etc.
Indicate data items relating to both patients and practices if relevant, including Read Codes (see appendix), age, sex, co-morbidity, prescriptions, tests and investigations.

The following information will be required for the analyses:

- age and gender of all young people in the database
- dates of registration & de-registration (transferred out date) of all young people in the database
- all drug prescriptions including ATC Classification Code and date of prescription
- indication, dosage and formulation (for the five most frequently prescribed drugs (by prevalence) in each ATC Therapeutic Level).
- Problems and diagnoses
- Consultations, specialist referrals related to treatment or conditions

9. ANALYSIS OF THE STUDY

Describe the approaches to be taken in analysis, including the statistical techniques to be applied.

Descriptive analysis will be conducted for patient demographics and prescription data. To describe the study cohort, the age and gender distribution and total person years of patients will be calculated. Time-trend analyses, age-specific and gender-specific drug measure estimates, consultations and specialist referrals will be assessed.

Prevalence will be defined as the number of youths who received one or more prescriptions for the drug classes divided by the person time of young people who are present in the database. As the prevalence varies depending on the duration of follow-up for each individual, prevalence will be calculated for each calendar year (annual prevalence). Ninety-five percent confidence intervals of prevalences will be calculated based on the Poisson distribution. Overall prevalence will be calculated for the entire study period by adding the numbers of youths who received one or more prescriptions of the drug classes and dividing by the total person time of the study population.

In addition to prescription data, information on problems, diagnoses, consultations and specialist referrals will also be investigated. These data can provide in-depth understanding on GP practice patterns and disease management in primary care.

<u>ATC Anatomical & Therapeutic level prescriptions</u>

Annual prevalences and overall prevalence by drug classes based on the ATC Anatomical and Therapeutic levels will be presented by age and gender.

<u>ATC C level (molecule) prescriptions:</u>

For the ATC Therapeutic levels A, D, H, J, P, C, N, M, R and L, overall prevalence will be estimated for each generic drug (ATC Chemical level) and presented by age and gender. On the basis of these prevalences, the five most frequently prescribed drugs per ATC Therapeutic Level will be retrieved and the following analysis applied:

1. Dosage and formulation

   Mean dosage, Standard Deviation and 25th, 50th and 75th percentiles will be calculated and presented by ATC Chemical level, formulation and age.

2. Indications

   To obtain insight into the medical conditions of the children and how they are treated, the indications for drug prescriptions will be derived from the linked indication and presented by ATC Chemical level, age and gender.

3. Incidence

   A child will qualify as incident user if he/she has not received a prescription for the drug under study in the previous year. The incidence rate will be the number of children with a first prescription of a drug during follow-up divided by the number of person-years or the number of children attributing to the study cohort during follow-up. Incidence rates will be given by calendar year, age and gender.

4. Number of prescriptions and treatment duration

For each prevalent and each incident user, the number of prescriptions will be calculated. For incident users, the treatment duration will be calculated from the prescribed quantity and prescribed daily dosage. Prescriptions will be combined with a maximum gap of 90 days.

Problems, consultations and referrals

The problems, consultations and referrals are coded using the Read code and ICD 10 classification. A treatment or condition which is linked to problems, consultations or specialist referrals will be investigated.

Data manipulation and analysis will be conducted using STATA/SE 11.0 for Windows (StataCorp LP, Texas, USA).

10. DISSEMINATION STRATEGY

List the journals and presentations in which it is intended that the results of the study will be published, and indicate whether and how the results of the study are likely to be used commercially.

It is planned that a number of papers will be published from this study, primarily in the following journals, reports and conferences:

- British Medical Journal
- Pediatrics
- British Journal of Clinical Pharmacology
- Archives of Disease in Childhood
- Pharmacoepidemiology and Drug Safety

The results will be used solely for research purposes.

11. INDICATE ANY ETHICAL PROBLEMS THAT YOU ENVISAGE

List those ethical issues not raised so far that might be important or present particular difficulties with the proposed study. Please also list any other information which you consider would be helpful to ISEAC.

None known

Signature of Applicant(s)

.... Date 16/03/2011.................................

.... Date ....

ISEAC DECISION

Signed .... Date ....

(Chairman)

COMMENTS

Appendix 9: IMS ethics approval letter

ims

10 October 2008

Professor Ian Wong
Centre for Paediatric Pharmacy Research
The School of Pharmacy, University of London,
First Floor , BMA House,
Tavistock Square,
London,
WC1H 9JP

Dear Ian,

I am writing to confirm that the Centre for Paediatric Pharmacy Research has submitted a protocol to the Independent Scientific and Ethics Committee established to review uses of the IMS Disease Analyzer database. The Committee approved the use of the database for drug utilisation studies in children as described in that protocol.

Yours sincerely

Peter Stephens
VP Public Health Affairs Europe, Middle East & Africa,
IMS Co-ordinator for ISEAC
IMS Health®
7 Harewood Avenue
London, NW1 6JB, UK
Tel: +44 207 393 5323 Mobile: +44 (0)7711 148653
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Appendix 10: Ethics approval from UCL School of Pharmacy Ethics Research Committee

Research Ethics Committee

Application Form REC/A (for MPharm and MSc projects)

The School of Pharmacy
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Mezzanine Floor, BMA House
Tavistock Square
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T 020 7874 1270
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www.pharmacy.ac.uk

Submission and review

Internal peer-review of research projects with a focus on ethical issues

This procedure for internal peer-review of projects, with a focus on ethical issues, should be followed for:

- *studies involving human subjects, data or material*
- *studies that would not be subject to review by the NHS*
- *studies that are designated 'evaluation of services' or 'audit'*

The purpose of the procedure is to ensure that all projects (excluding literature reviews) have the benefit of an independent review and that all students, irrespective of the type of study they are conducting, gain an appreciation of the issues and processes of ethical review.

For more information and guidance see www.pharmacy.ac.uk/ethics.html

Three forms are contained in this application and all must be completed:

1. **Project information form (REC/A/1)**
2. **Review of ethical issues (REC/A/2)**
3. **Peer review form (REC/A/3)**

You must complete the project information form (REC/A/1) and the review of ethical issues (REC/A/2). If you are preparing an **information leaflet** for your participants, please also attach this to your application.

The two completed forms and any attachments should then be reviewed by your academic supervisor at The School of Pharmacy who should complete the peer review form (REC/A/3). Your academic supervisor should then ensure that your application is also independently reviewed, usually by another member of staff in your Department who is not involved in supervision of your project.

Finally you should address any issues raised by your supervisor and the independent reviewer, and include details of how you have dealt with these in the form (REC/A/3). Please see flowchart below, which outlines the process.

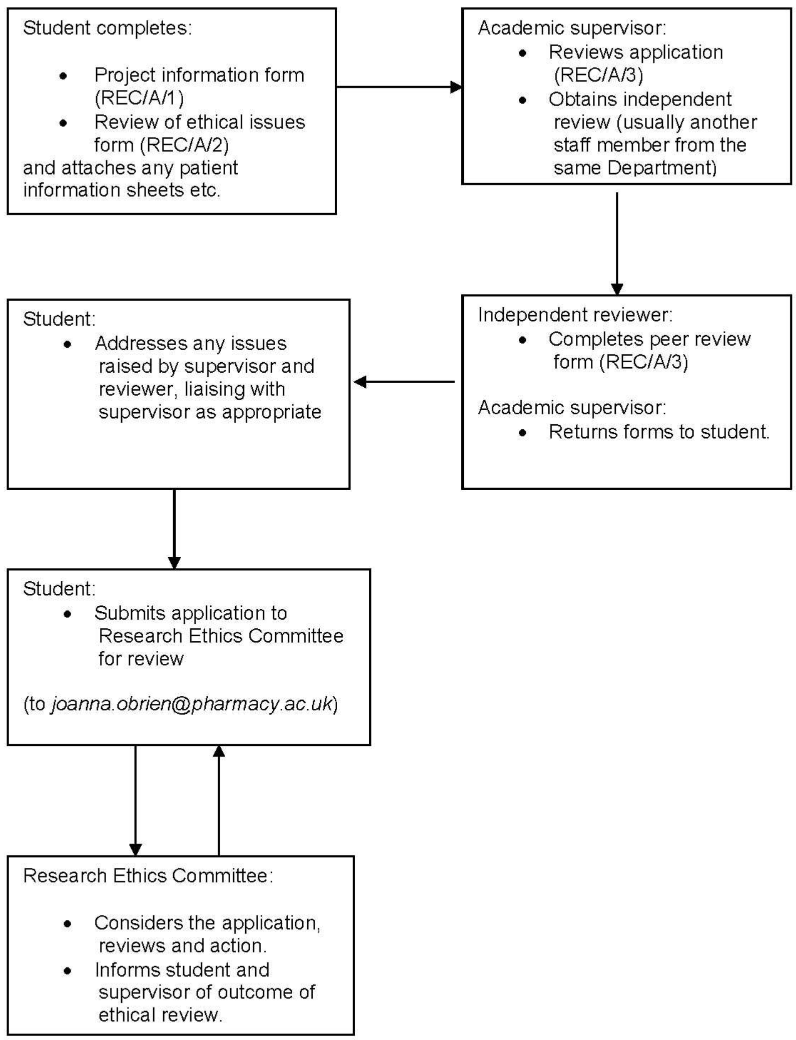
Please note that group projects may be submitted as one application.

All three forms must be submitted together by e-mail to joanna.obrien@pharmacy.ac.uk

Outcome of Research Ethics Committee consideration

The Research Ethics Committee will confirm the outcome of its consideration within 10 working days. The outcome will be one of the following options: approval; approval with minor revision; further information required; resubmission required.

Flowchart of ethical review process



REC/A/1/

Project Information Form

Title of project: Service evaluation: Effectiveness of secondary care weight management for children and adolescents
Name of applicant(s): Iao Chon Lei
Name of academic supervisor at The School of Pharmacy: Professor Ian wong Yingfen Hsia Dr Billy White Dr Russell Viner
Date of submission: **11/03/2001**
Is this a resubmission? ☐ yes (please detail specific changes from original submission) ☒ no
Planned start date for project work: 01/03/2011
Please give the following information about the project:
• **Brief introduction and background to the project**
Obesity can be caused by a number of factors such as unhealthy diet (high sugar, fatty food intake) and lack of physical activity where the factor of psychological may also play an important role. Long term could lead to serious conditions such as hypercholesterolaemia and diabetes, therefore correct and immediate therapy before significant damage is caused to the patient is essential. The usual diagnosis is measurement of body mass index (BMI) in relation to height and weight with specific ranges that refer to different levels such as normal, overweight or obese. Evidence has shown that Obesity in children and adolescents has increased worldwide. A UK study has demonstrated that anti-obesity drug prescribing dramatically increased 15-fold between 1999 and 2006 in young people in primary care (Viner et al., 2009). In 2006, NICE (the National Institute for Health and Clinical Excellence) suggested the incorporation of other aspects such as lifestyle interventions including psychological, physical activity and diet as first line treatment. Pharmacological treatment such as orlistat and sibutramine should be considered as adjuncts to lifestyle interventions in adolescents above the age of 12 with comorbidities, and the use under 12 years of age only for those with life-threatening comorbidities (NICE 2006). In January 2010, the European Medicines Agency (EMA) recommended removing sibutramine from all markets in the European Union (EU) due to the risk of cardiovascular events in adults. Consequently orlistat is the only licensed anti-obesity drug in the UK. To date, there is insufficient evidence for the effectiveness of weight management in young people in UK secondary care. Therefore, this project aims to examine the patterns of use of pharmacological interventions and behavioral interventions with relation to overweight and/or obese children and adolescents in the paediatric obesity clinic at University College London Hospital (UCLH).

- **Clear statement of the research question and aims and objectives**

Research question:
Do weight management programmes (pharmacological, behavioural intervention) lead to body weight, BMI, or adiposity reduction in overweight and obese children and adolescents in secondary care?

Aims:
To evaluate the effectiveness and patterns of use of weight management programmes (pharmacological, behavioural intervention) in overweight and obese children and adolescents.

Objectives:

- To complete the 4 year paediatric obesity data collection from January 2007 to December 2010 in UCLH paediatric obesity clinic.
- To identify anti-obesity drug prescribing trends in the database.
- To identify behavioural interventions (e.g. psychological intervention, diet) as obesity therapy.
- To identify variables that could affect treatment outcome.

- **Study design and methods (e.g. sampling strategy and recruitment; justification of sample size; data collection and instruments; outcome measures; data processing and analysis)**

Method

The project will be a service evaluation to judge and define current care involving extensive existing database analysis, whereby the data will be retrospectively collected in paediatric obesity clinic at UCLH from January 2007 to December 2010. All children and adolescents aged under 20 years of age during the study period will be included in this study.

As this study is a descriptive and quantitative study, a sample size calculation will not be required. The outcome of interest includes identification of anti-obesity drug prescribing trend, BMI and fat mass changes in pharmacological and behavioral interventions.

Data analysis will be aimed at specific questions identified. Data will be represented in clearly state graphs with descriptive analysis of each study question. The data will be used to identify prescribing trend that can be represented through a graph during the study period, other data such as the outcome based on the BMI, fat mass will be described and represented as before and after, with possible intervals from start to end, and follow up appointments.

- **Anticipated outcomes and intended value**

- Provide information on the effectiveness of weight management in UCLH paediatric obesity clinic.
- Identifying potential variables that could impact pharmacological and behavioural intervention on weight management in young people
- Planned paper submission to an international medical journal for publication

- **Any other relevant information**

Review of Ethical Issues (REC/A/2)

This review looks at the ethical issues relevant to the project using the Foster framework[1]. This involves the application of three perspectives to the identification and consideration of ethical issues. The form presents three sets of questions that can be used as a guide to identify and address these issues. Please answer all questions that are relevant to the project, describe the issues that arise and how these will be addressed.

Questions to address from a goals-based perspective:

Comment on why the research is important and the anticipated value or application of the findings.

- Why is this study important?
- Justify your study design and methods – why is this the best way to achieve your objectives?
- Comment on the likely strength of your findings. To what extent do you think they will be representative and accurate?

Due to the limited drug choice available as treatment for childhood obesity, it is important to further expand on the knowledge of safety and effectiveness of pharmacological and behavioural therapy in paediatric weight management clinic. As there are many potential variables (gender, age, ethnicity), that could potentially impact on the final outcome of therapy in weight management, it is important to analysis those variables with regard to treatment outcome (e.g. BMI, fat mass). This can improving secondary care management and allow clinicians to provide the best treatment and care for individuals based on the variables.

The study will be conducted through analysis of 4 year database (January 2007 to December 2010) to provide a more representative data. By collecting retrospective data allows me to directly isolate important data required for the study such as patient's demographic data such as age, gender, ethnicity which are important variables, others include consultants the patients seen, BMI (as the outcome) can all be identified.

The study should provide a representative data. If successful, the result will provide the foundation for further questions of which variable influences the outcome of therapy in weight management clinics. The result will be reliable as the study includes a large sample size over a period of at least 12 months to provide follow-up appointments.

[1] Foster C (2001) *The Ethics of Medical Research on Humans*. Cambridge: Cambridge University Press

Questions to address from a duty-based perspective:
Comment on what you are asking of research subjects, how reasonable this is and how you will address any concerns they might have.

- Is what you are asking of your respondents/ participants reasonable?
- What will participating in the research involve?
- How much time will it require?
- How intrusive might any interview, questionnaire, observation, or other data collection be?
- What will you do with the information?
- What are the risks to participants? Are they acceptable?
- What are the risks to you in carrying out the research? Are they acceptable?
- What happens if someone complains or something goes wrong?

The project does not involve direct patients contact or any respondents and participants for study. The project is conducted through data analysis from databases in paediatric obesity clinic at UCLH without any risk that involve participants, as it does not involve interviews or direct surveys.

The patient's data and clinical information will only be accessed through UCLH premises under clinical supervision (Dr Billy White) and any patient identifiable data will not be included in my project report. Furthermore, I will complete and obtain an Honorary Contract with CRB check that proves my status for access to patient records and other information. The data will remain within the UCLH premises and will not be removed from the hospital therefore I will not be held liable if things go wrong. Moreover, any data used will be safely stored within an encrypted memory stick whereby data has been made anonymous with unique identification codes to ensure safe keeping of sensitive data.

Questions to address from a rights-based perspective:

Can participants make an entirely voluntary and informed choice about whether or not to take part?

• Is an information leaflet supplied that conforms to accepted guidelines? (if so, please attach this to your form) • Is there an opportunity to ask questions? • What steps will you take to ensure confidentiality/ anonymity (e.g. with regard to data protection legislation)? • Are potential participants free to make their own decision: e.g., time to decide, no incentives, concerns about consequences or taking/not taking part or feelings of obligation?
My project will not involve participants. My data analysis will be conducted under supervision and information will not be removed from the UCLH premises, and any data stored will be made anonymous with allocation of unique identification codes to ensure the sensitive and confidential data not being lost or fallen into un-responsible individuals.

Reference:

Park, M. H., S. Kinra, K. J. Ward, B. White & R. M. Viner. 2009. Metformin for obesity in children and adolescents: a systematic review. In *Diabetes Care*, 1743-5. United States.

Viner, R. M., Y. Hsia, A. Neubert & I. C. Wong. 2009. Rise in antiobesity drug prescribing for children and adolescents in the UK: a population-based study. In *Br J Clin Pharmacol*, 844-51. England.

NICE guidelines - guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children, issued date December 2006.

European Medicines Agency (EMEA). Questions and answers on the suspension of medicines containing sibutramine. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sibutramine_107/WC500094238.pdf (Accessed March 2011)

Peer Review Form for MPharm and MSc Projects (REC/A/3)

Title of project: Service evaluation: Effectiveness of secondary care weight management for children and adolescents
Name of applicant(s): Iao Chon Lei
Name of academic supervisor: Professor Ian Wong, Yingfen Hsia, Dr. Billy White, Dr. Russell Viner
Date of submission: 10/03/2010
Name of independent reviewer: Dr. Liz Jamieson
Date of review:

Comments of independent reviewer:
I am not entirely sure this project is service evaluation on several grounds (perhaps you should speak to someone from R&D to see how they would classify it):

(a) You are introducing research questions in terms of looking at the effectiveness of different interventions.
(b) You state that there are "many potential variables (gender, age, ethnicity), that could potentially impact on the final outcome of therapy in weight management and it is important to analysis those variables with regard to treatment outcome (e.g. BMI, fat mass)". This would be hypothesis testing. If this is service evaluation, what standards are you evaluating the service against?
(c) A service evaluation normally includes interview/surveys to ascertain how users of a service perceive its effectiveness
(d) Who set up and maintains the obesity database you are using and how can you be sure it is accurate? You may need to obtain permission from key staff, e.g. Clinical Director for access to this data.Will all the obesity management data be on this database, i.e. you will not be collecting any additional data and you are not making any attempts to verify this data or add to it from patient notes?
(e) On page 5, please explain why these variables (age, gender, ethnicity) are important. Any evidence has shown these variables related to obesity treatment outcome

Comments of academic supervisor:
Please address the following comments:

1. **Data analyses are based on the objectives you stated in the method section.**
2. **On page 5, please explain why these variables (age, gender, ethnicity) are important. Any evidence has shown these variables related to obesity treatment outcome?**

How has the applicant addressed the comments of the supervisor and the independent reviewer?

I will not be analysing the effectiveness of the different interventions, rather I will be describing the use of different medications. Service evaluations are necessary to measure outcomes. Outcomes of clinical services are increasingly important in healthcare provision and are necessary to justify resources allocated to them. This work is part of a wider service evaluation that will include patient participation but this project does not have the scope to include such work.

This is primarily a service evaluation rather than an audit as there are no gold standards relating to prescribing or referral patterns, or service outcomes.

At present there is only 1 anti-obesity drug recommended by NICE (National Institute of Clinical Excellence) yet little is known about its use within clinical settings, with evidence only available from primary care (ref Hsia). Metformin is also widely used for weight management however its use has not been described within a clinical setting. The description of current prescribing patterns will form the basis of further work involving service users.

Data is currently maintained in various formats:

1. Hospital electronic records contain copies of correspondence to other health professionals which should include details of medication use, together with data on weight, height and blood pressure
2. A database developed and maintained by Dr Russell Viner, Clinical Lead of Obesity service, contains data as outlined above for patients under his care. This is stored on UCLH servers with access limited to paediatric services.
3. Individual electronic weight and height records for each patient stored on shared folder. This is stored on UCLH servers with access limited to paediatric services.
4. Patient paper records: these are stored outside London and due to logistical difficulties, they will not be used where data is available from sources 1-3.

Data will be checked with a clinician (Dr Billy White) if there are any queries. Permission has been granted by the clinical lead for the Adolescent Weight Management Service, Dr R Viner to perform this service evaluation using the above data sources and JL has an honorary contract at UCLH.

I will not be analysing the association between age, gender or ethnicity and service outcome.

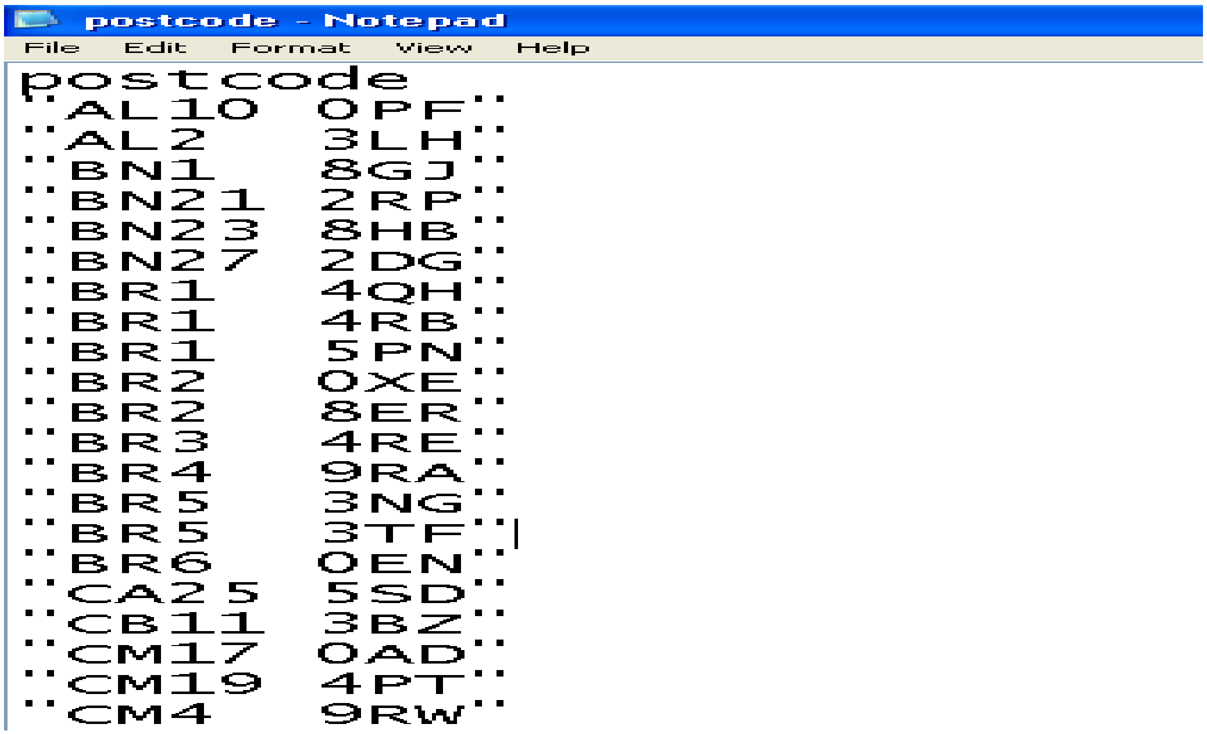
Appendix 11: Index of Multiple Deprivation Domain Indicators (IMD) (taken from English Indices of Deprivation Technical Report: http://www.communities.gov.uk/publications/corporate/statistics/indices2010technicalreport) [last accessed 01/09/2012]

1. Income Deprivation Domain indicators:
• Adults and children in income support families
• Adults and children in income-based Jobseeker's Allowance families
• Adults and children in Pension Credit (Guarantee) families
• Adults and children in Child Tax Credit families (who are not claiming income)
• Support, income-based Jobseeker's Allowance or Pension Credit) whose equivalised income (excluding housing benefits) is below 60% of the median before housing costs
• Asylum seekers in England in receipt of subsistence support, accommodation support, or both
2. Employment Deprivation Domain indicators:
• Claimants of Jobseeker's Allowance (both contribution-based and income based), women aged 18-59 and men aged 18-64
• Claimants of incapacity benefit aged 18-59/64
• Claimants of Severe Disablement Allowance aged 18-59/64
• Claimants of Employment and Support Allowance aged 18-59/64 (those with a contribution-based element)
• Participants in New Deal for 18-24s who are not claiming Jobseeker's Allowance
• Participants in New Deal for 25+ who are not claiming Jobseeker's Allowance
• Participants in New Deal for Lone Parents aged 18 and over (after initial interview)
3. Health Deprivation and Disability Domain indicators:
• *Years of Potential Life Lost*: An age and sex standardised measure of premature death
• *Comparative Illness and Disability Ratio*: An age and sex standardised morbidity/disability ratio
• *Acute morbidity*: An age and sex standardised rate of emergency admission to hospital
• *Mood and anxiety disorders*: The rate of adults suffering from mood and anxiety disorders
4. Education, Skills and Training Deprivation Domain indicators:
• Key Stage 2 attainment: The average points score of pupils taking English, maths and science Key Stage 2 exams
• Key Stage 3 attainment: The average points score of pupils taking English, maths and science Key Stage 3 exams
• Key Stage 4 attainment: The average capped points score of pupils taking Key Stage 4 (GCSE or equivalent) exams
• Secondary School absence: The proportion of authorised and unauthorised absences from secondary school

• Staying on in education post 16: The proportion of young people not staying on in school or non-advanced education above aged 16
• Entry to higher education: The proportion of young people aged under 21 not entering higher education
• Adult skills: The proportion of working age adults aged 25-54 with no or low qualifications
5. Barriers to Housing and Services Domain indicators:
• Household overcrowding: The proportion of all households in an LSOA which are judged to have insufficient space to meet the household's need
• Homelessness: The rate of acceptances for housing assistance under the homelessness provisions of housing legislation
• Housing affordability: The difficulty of access to owner-occupation, expressed as a proportion of households aged under 35 whose income means that they are unable to afford to enter owner occupation
• Road distance to a GP surgery: A measure of the mean distance to the closest GP surgery for people living in the LSOA
• Road distance to a food shop: A measure of the mean distance to the closest supermarket or general store for people living in the LSOA
• Road distance to a primary school: A measure of the mean distance to the closest primary school for people living in the LSOA
• Road distance to a Post Office: A measure of the mean distance to the closest post office or sub post office for people living in the LSOA
6. Crime Domain indicators:
• Violence: The rate of violence (19 recorded crime types) per 1000 at-risk population
• Burglary: The rate of burglary (4 recorded crime types) per 1000 at-risk properties
• Theft: The rate of theft (5 recorded crime types) per 1000 at-risk population
• Criminal damage: The rate of criminal damage (11 recorded crime types) per 1000 at-risk population
7. Living Environment Deprivation Domain indicators:
• Housing in poor condition: The proportion of social and private homes that fail to meet the decent homes standard
• Houses without central heating: The proportion of houses that do not have central heating
• Air quality: A measure of air quality based on emissions rates for four pollutants
• Road traffic accidents: A measure of road traffic accidents involving injury to pedestrians and cyclists among the resident and workplace population

Appendix 12: Steps of obtaining the IMD 2007 of Lower Super Output Area ranking and score

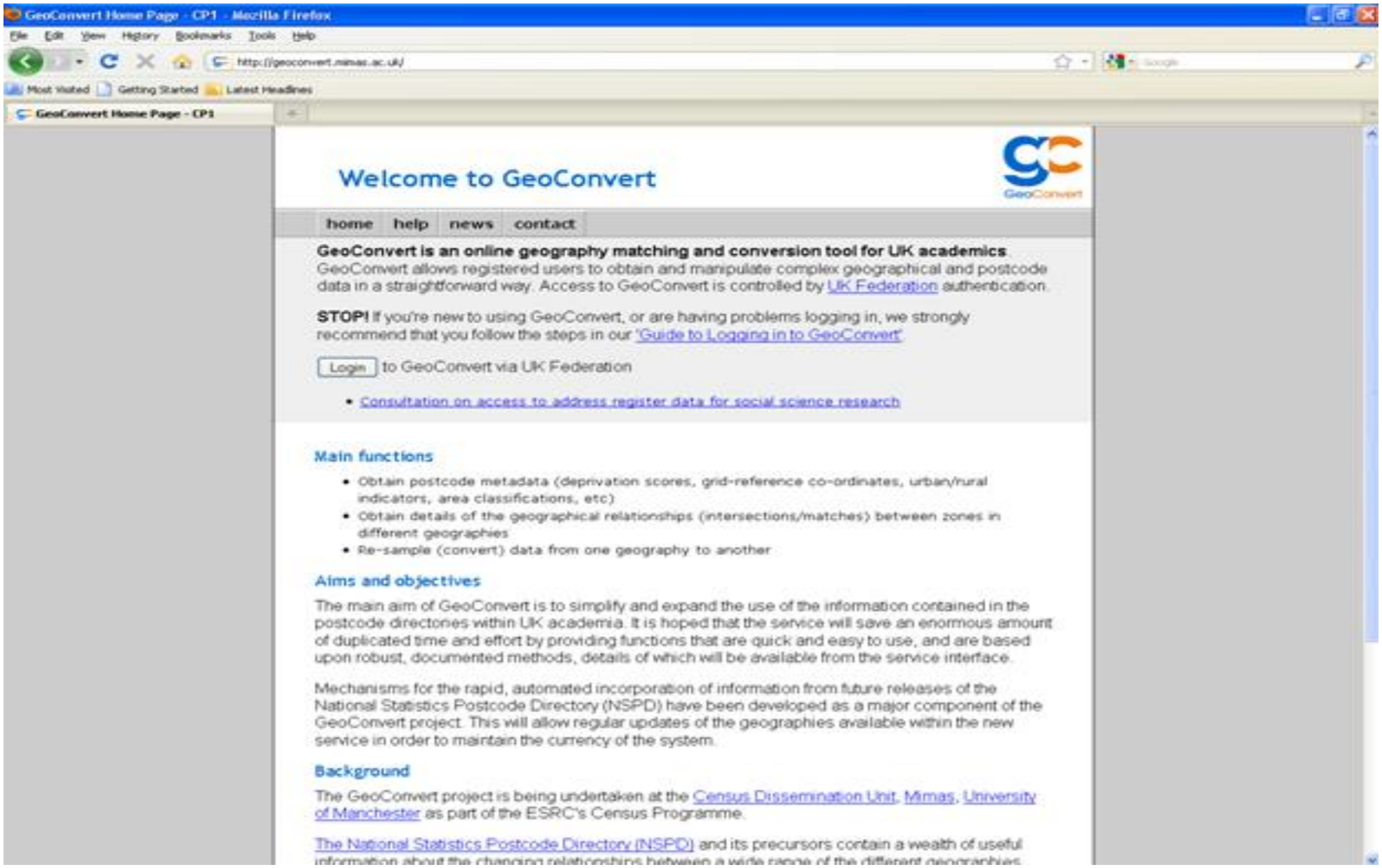
Step 1: Compile a list of all patients' postcodes


postcode - Notepad

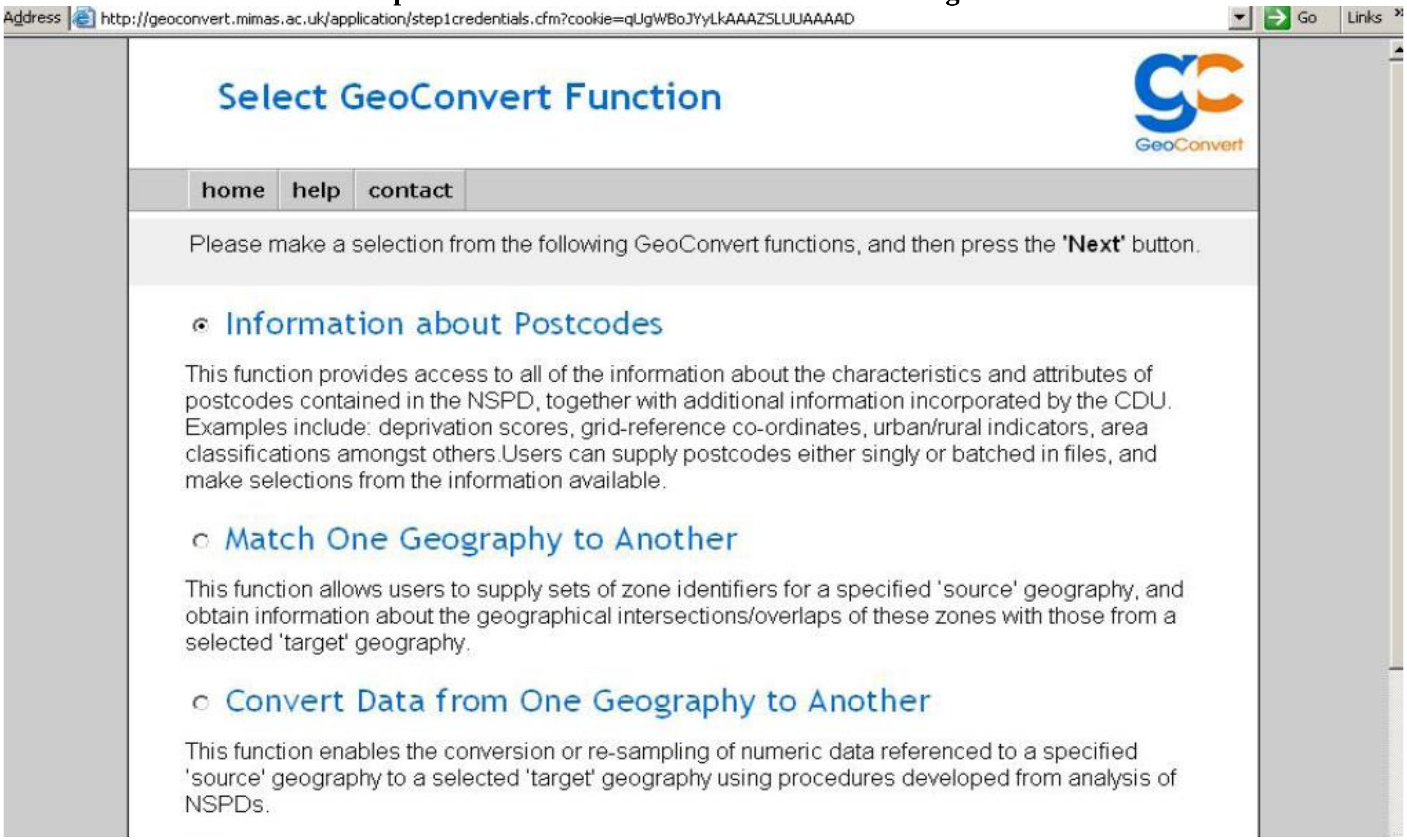
File Edit Format View Help

postcode
"AL10 0PF"
"AL2 3LH"
"BN1 8GJ"
"BN21 2RP"
"BN23 8HB"
"BN27 2DG"
"BR1 4QH"
"BR1 4RB"
"BR1 5PN"
"BR2 0XE"
"BR2 8ER"
"BR3 4RE"
"BR4 9RA"
"BR5 3NG"
"BR5 3TF"
"BR6 0EN"
"CA25 5SD"
"CB11 3BZ"
"CM17 0AD"
"CM19 4PT"
"CM4 9RW"

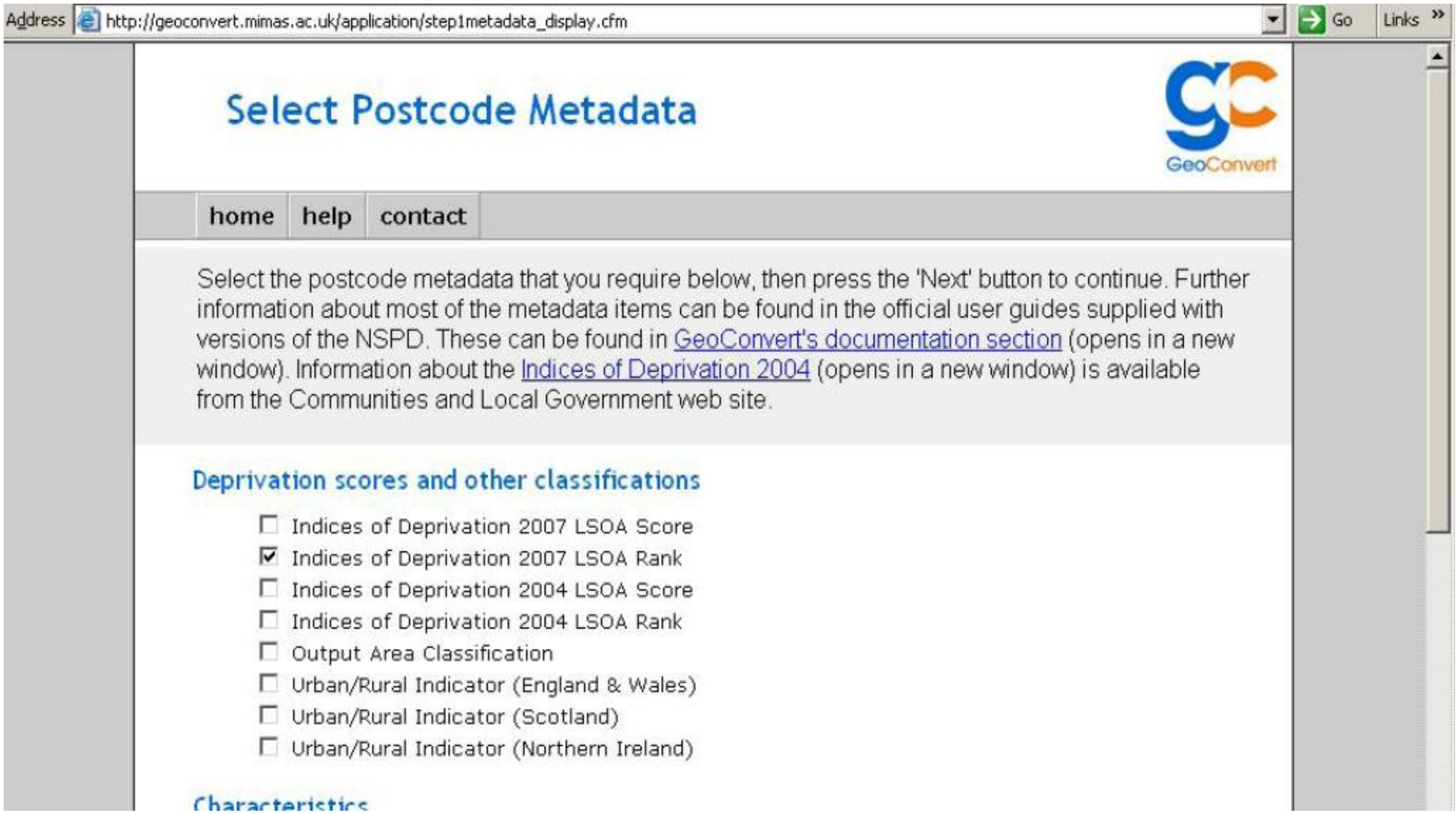
Step 2: Access to GeoConvert website



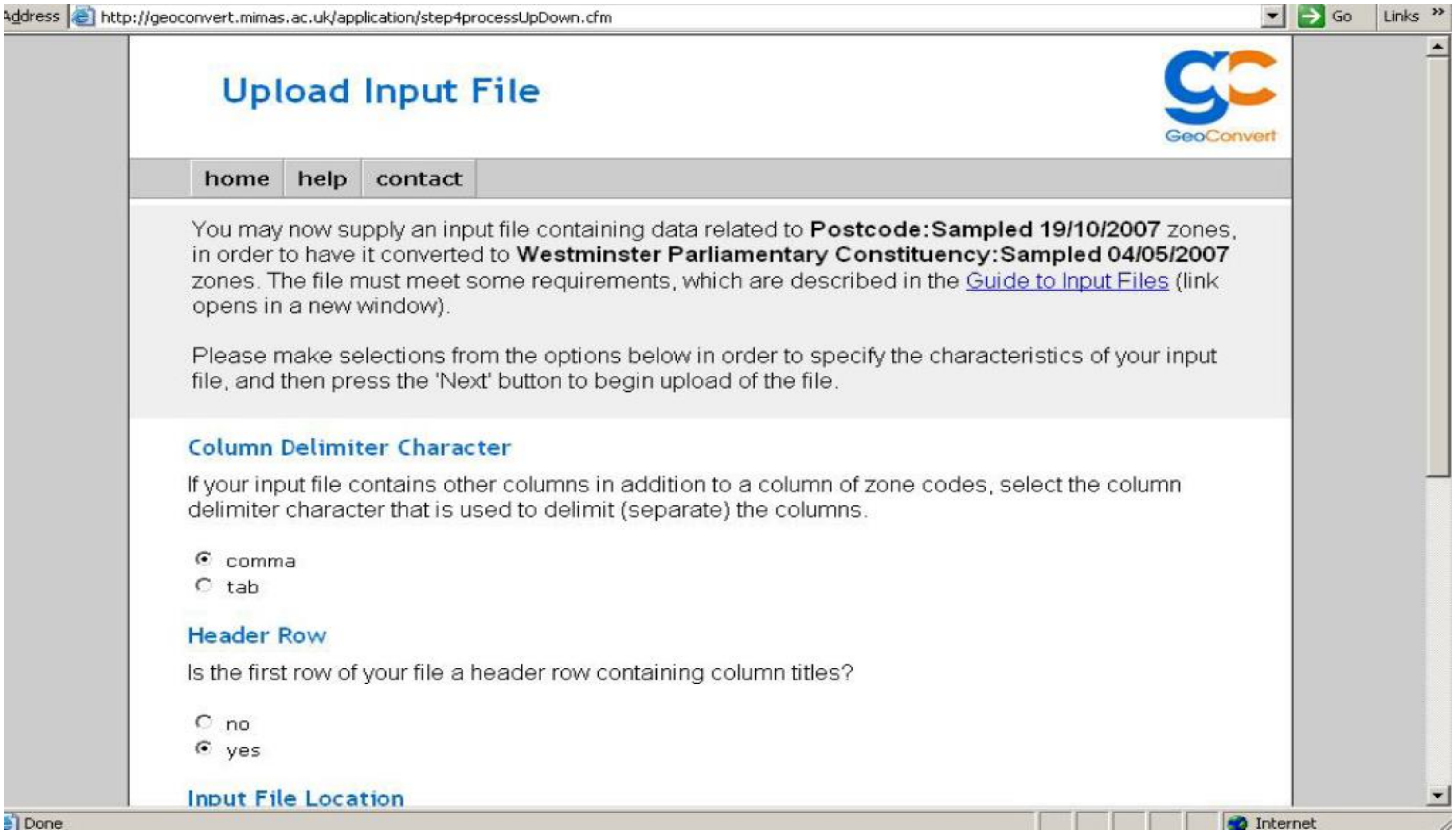
Step 3: Select the function to obtain IMD ranking and score



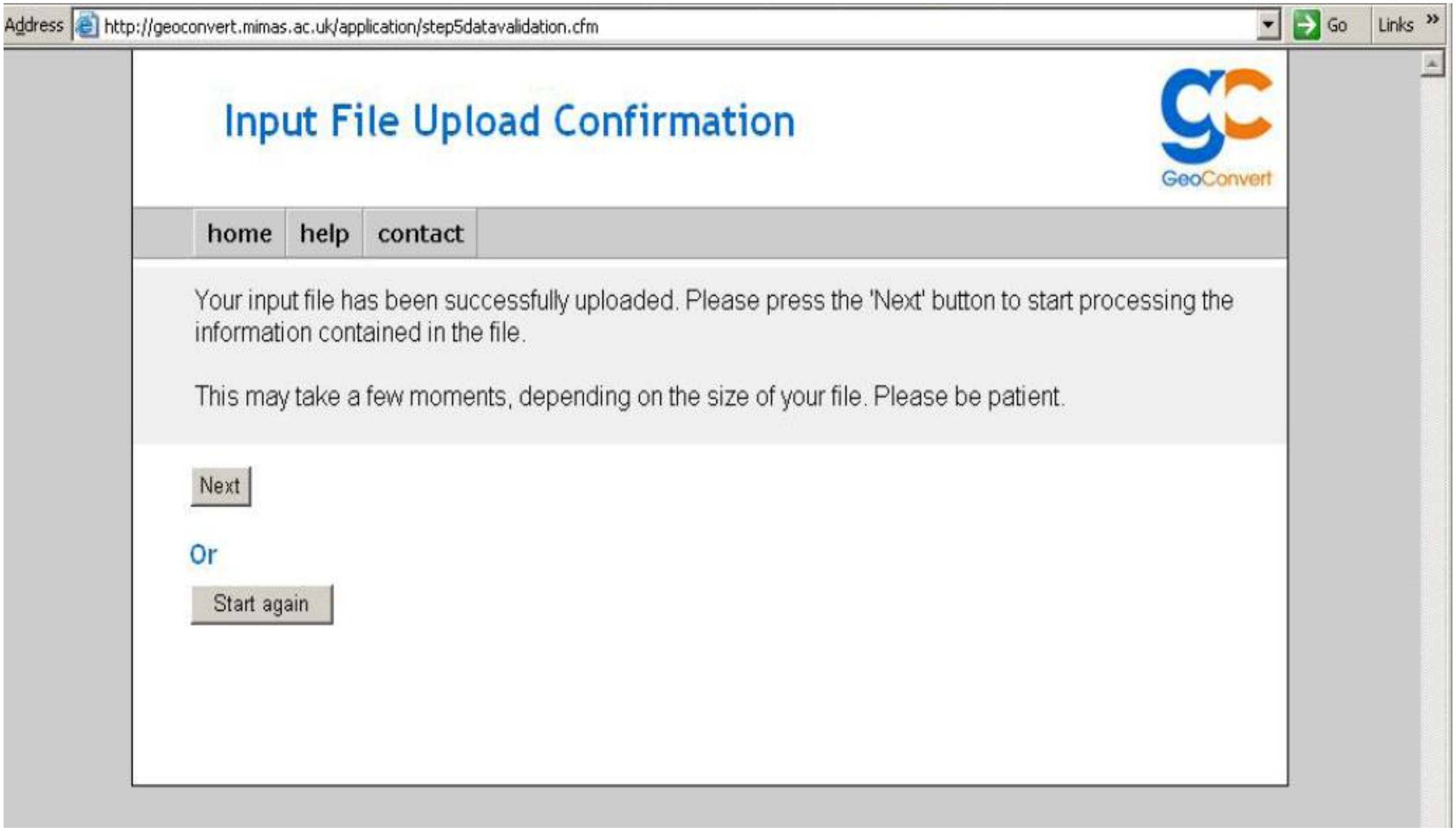
Step 4: Select IMD 2007 Rank and Score classification



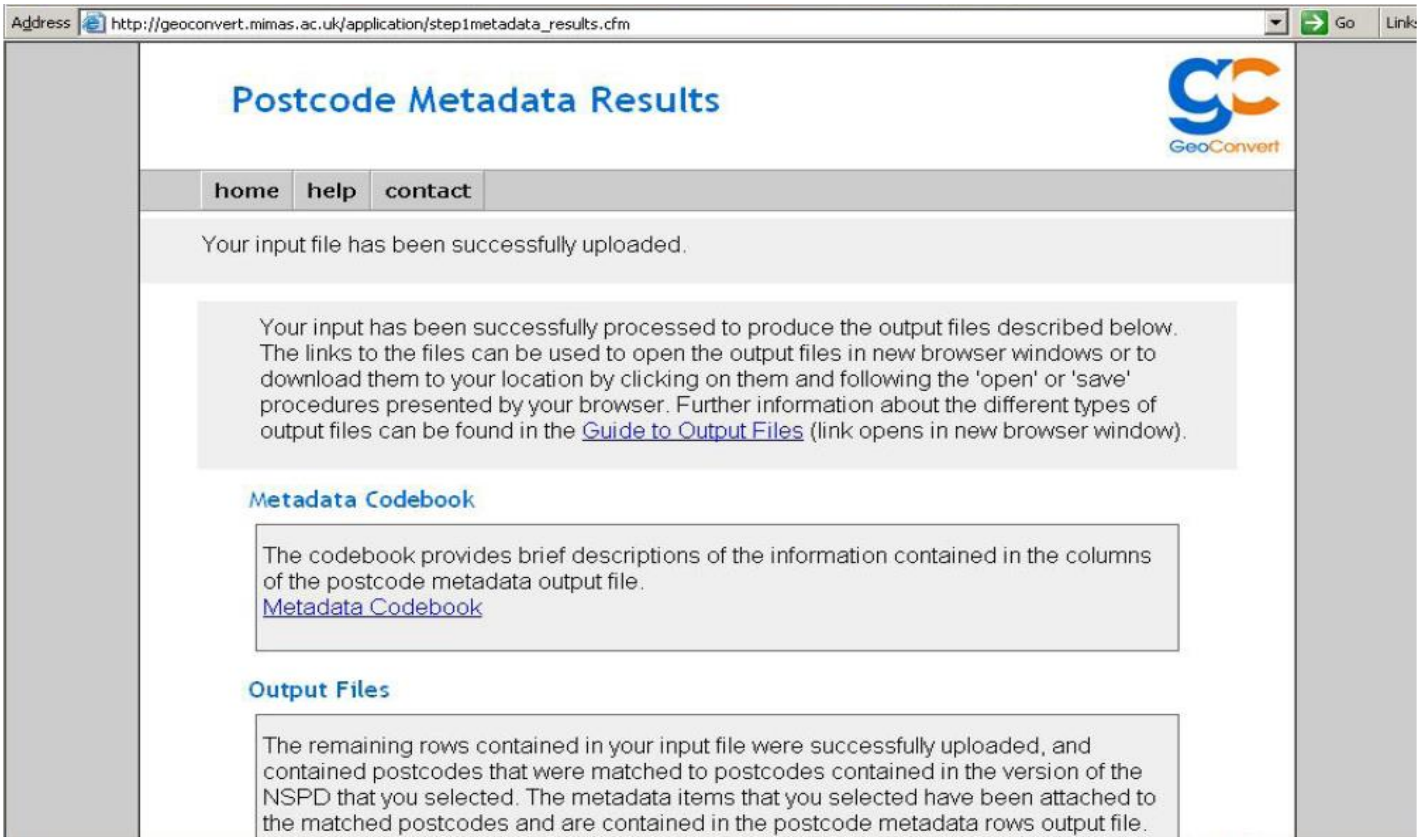
Step 5: To upload the list of postcode



Step 6: The completion of file uploading



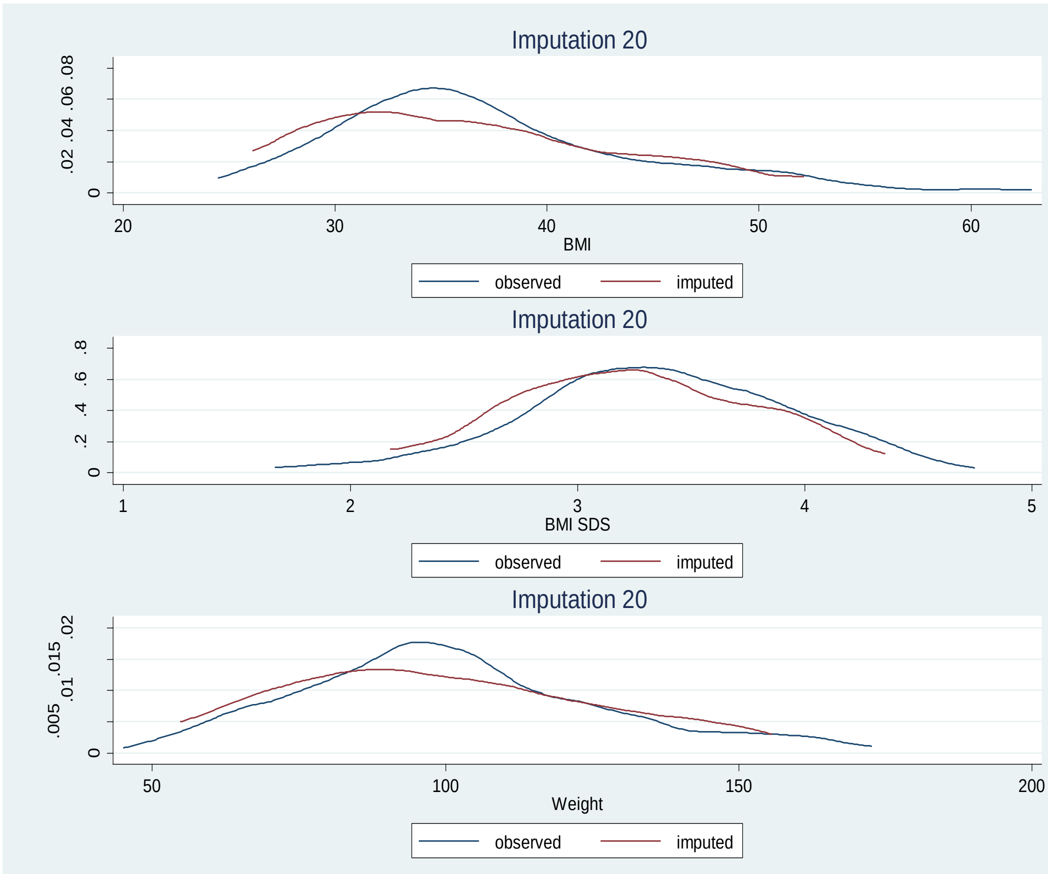
Step 7: Download the results



Step 8: Results of IMD 2007 ranking and score for included patients

	A	B	C	D	E	F	G
1	input_row	standard_postcode	IMD_200710nc	IMD_2007_RANK10nov	input_postcode		
2	2	DA3 7LF	4.82	30097	DA3 7LF		
3	3	BR2 8ER	19.2	14570	BR2 8ER		
4	4	BR2 8ER	19.2	14570	BR2 8ER		
5	5	N7 9DZ	54.65	1531	N7 9DZ		
6	6	N7 9DZ	54.65	1531	N7 9DZ		
7	7	N7 9DZ	54.65	1531	N7 9DZ		
8	8	N7 9DZ	54.65	1531	N7 9DZ		
9	9	N7 9FB	54.65	1531	N7 9FB		
10	10	NW5 2UG	40.09	4633	NW5 2UG		
11	11	NW5 2UG	40.09	4633	NW5 2UG		
12	12	N6 6EL	14.82	18366	N6 6EL		
13	13	N6 6EL	14.82	18366	N6 6EL		
14	14	N1 7ES	32.78	7066	N1 7ES		
15	15	EC1V8EJ	46.03	3098	EC1V 8EJ		
16	16	SS2 6QY	36.69	5680	SS2 6QY		
17	17	N19 5DX	51.82	1981	N19 5DX		
18	18	N19 5DX	51.82	1981	N19 5DX		
19	19	N19 5DX	51.82	1981	N19 5DX		
20	20	BR5 3NG	27.22	9461	BR5 3NG		
21	21	BR5 3NG	27.22	9461	BR5 3NG		
22	22	BR5 3NG	27.22	9461	BR5 3NG		
23	23	LU1 3UP	38.74	5047	LU1 3UP		
24	24	LU1 3UP	38.74	5047	LU1 3UP		
25	25	N1 0EF	30.15	8127	N1 0EF		

Appendix 13: Distribution of observed and imputed BMI, BMI SDS, and weight at 6 months follow up data



Two-sample Kolmogorov-Smirnov test for equality of distribution functions: BMI

Smaller group	D	P-value	Corrected
0:	0.0797	0.761	
1:	-0.1584	0.340	
Combined K-S:	0.1584	0.653	**0.562**

Two-sample Kolmogorov-Smirnov test for equality of distribution functions: BMI SDS

Smaller group	D	P-value	Corrected
0:	0.0325	0.956	
1:	-0.2029	0.170	
Combined K-S:	0.2029	0.339	**0.257**

Two-sample Kolmogorov-Smirnov test for equality of distribution functions: weight

Smaller group	D	P-value	Corrected
0:	0.0649	0.822	
1:	-0.1187	0.519	
Combined K-S:	0.1187	0.899	**0.851**

Appendix 14: Publications from this thesis